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Clinical Studies

Cyclical Edema and Shock Due to Increased Capillary Permeability
Bayard Clarkson, David Thompson, Melvin Horwith and E. Hugh Luckey 193

This is a detailed report of an extraordinary case, quite without parallel in the literature and yet probably reflecting in the extreme what may well occur normally in some slight degree. At the age of thirty-two the patient, previously well, began to have periodic episodes of edema and shock, abrupt in onset and coinciding with premenstrual periods. Exhaustive studies, continued until her death at the age of thirty-four, established the immediate pathogenesis of these episodes—sudden extravasation of plasma into the extravascular compartments—but no underlying cause of the cyclical porosity of the capillaries was discovered.

The Relation of Emotional State to Renal Excretion of Water and Electrolytes in Patients with Congestive Heart Failure
Robert Barnes and William W. Schottstaedt 217

An instructive study which expresses in concrete numbers what is generally if vaguely apparent, that patients with congestive heart failure in precarious compensation may decompensate when subjected to certain emotional stresses. It is shown that depression and tension cause retention of salt and water; excitement, anger and apprehension, on the other hand, elicit a sodium and water diuresis, at least temporarily. In fact these responses to emotional factors, so often ignored, may be more marked than the response to physical exertion, usually regulated with such great care. Thus the therapeutic value of reassurance and sympathy is at last statistically validated.

Effect of Shock and of Vasopressor Drugs on the Regional Circulation of the Brain, Heart, Kidney and Liver . . . Eliot Corday and John H. Williams, Jr. 228

Using direct methods of measurement of blood flow, the effects of shock and of vasopressors (levarterenol, metaraminol) on blood flow and vascular resistance in the dog were observed continuously and simultaneously in regions of particular clinical interest. The results in general conform with those previously obtained by indirect methods. As the systemic blood pressure fell (bleeding), blood flow through the internal carotid artery, anterior descending coronary artery, hepatic artery, portal vein and renal vein fell. When the blood pressure was restored by vasopressors, there was an increase in blood flow through the carotid, coronary and hepatic arteries, a

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What are the most common complications in pregnant diabetics?

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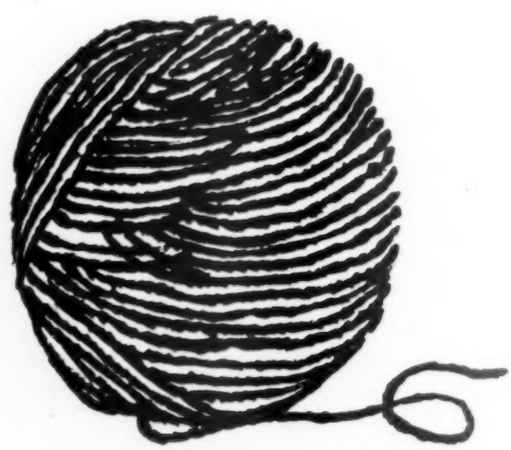
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*Duncan, G. G.: Diseases of Metabolism: Detailed Methods of Diagnosis and Treatment, ed. 4, Philadelphia, Saunders, 1959, p. 795.

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decrease in the portal (mesenteric) and renal veins. This redistribution of circulating blood volume has obvious advantages in maintaining blood flow through the vital areas of the brain and heart. There are disadvantages, however, which should not be overlooked in clinical application, points which are discussed in some detail.

Combined Aortic and Mitral Stenosis. A Clinical and Physiological Study
GORDON KATZNELSON, ROBERT M. JREISSATY, GILBERT E. LEVINSON, SAMUEL W. STEIN AND WALTER H. ABELMANN 242

A careful clinical and physiological study of twenty-two cases of combined aortic and mitral stenosis indicates that clinically the natural history is dominated by features of mitral stenosis in terms of onset, sex and chronicity. Angina, syncope and dizziness were infrequent. Physical signs of aortic stenosis were present, but electrocardiographic and radiologic features were absent. The reverse was true for signs of mitral stenosis. Severe mitral stenosis limited the left ventricular work and the gradient across the aortic valve. The study illustrates the value of left heart catheterization in defining the nature and extent of pathophysiologic alteration in valvular disease.

Renal Cortical Necrosis. Clinical and Pathologic Features in Twenty-One Cases
JACQUES D. WELLS, E. GORDON MARGOLIN AND EDWARD A. GALL 257

This is an account of a large and rather unusual experience with renal cortical necrosis, apparently including patients with focal necrosis which evidently may occur in a variety of situations having severe renal ischemia in common. The chief problem in differential diagnosis during life was separation from renal tubular necrosis, a more benevolent disorder in which suppression of urine is apt to be less complete, of lesser duration and more prone to spontaneous recovery. The fact that bilateral renal cortical necrosis is turning up more frequently of late in non-obstetrical services is sufficient reason for familiarity with the clinical manifestations of this still unexplained disorder.

Renal Tubular Necrosis Following Lesions of the Brain
PHILIP R. STEINMETZ AND JOHN E. KILEY 268

The authors make the point that injuries to the brain, notably those of the frontal lobe (which is closely related to the limbic system and therefore may be concerned with regulation of renal vasomotor activity), may be followed by acute tubular necrosis. Five cases are cited, although in some the renal shutdown was preceded by prolonged hypotension which, irrespective of the site of trauma, might have precipitated the renal injury.

Correlation of Lung Macrosections with Pulmonary Function in Emphysema
HERBERT C. SWEET, JOHN P. WYATT AND PETER W. KINSELLA 277

The authors have devised an ingenious method for correlation of emphysematous impairment of pulmonary function and structure. At necropsy, macrosections of the lung were prepared and scanned to give an estimate of morphological change; this was compared with functional estimates of the degree of emphysema obtained during life. The correlation was close enough to lend support to the validity of both methods of assessment.

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Metabolic and Radioactive Tracer Studies in Carcinoma of the Prostate. Effect of Diethylstilbestrol and of Orchiectomy
HERTA SPENCER, ROBERT EISINGER AND DANIEL LASZLO 282

This laborious metabolic study of patients with prostatic cancer and osteoblastic metastases brings out clearly the degree of calcium retention associated with the osteoplasia of this disorder (in contrast to other tumors with lytic lesions of the bones). The clinical improvement following estrogen therapy and orchiectomy was accompanied by corresponding changes in calcium balance and, in the case of orchiectomy, also by rather striking nitrogen retention. The significance of the alterations in calcium, phosphorus and nitrogen balance in these patients before and after treatment is reasonably discussed.

Hypersensitivity to Para-Aminosalicylic Acid
DAVID G. SIMPSON AND JANE H. WALKER 297

In view of the wide use of PAS as an antituberculous agent, its proneness to induction of hypersensitivity reactions becomes a matter of practical importance. Such reactions are usually delayed, not making their appearance until the fourth week of drug administration, and may be insidious at first but severe later. Fever and rash are most common, but the clinical and laboratory manifestations may be varied, as this study of a large number of cases attests. Hepatotoxicity is the most threatening complication of PAS therapy, and has resulted in fatality.

Suicidal Behavior in a General Hospital WILLIAM BROWN AND JOSEPH E. PISETSKY 307

This is a straightforward discussion of a problem which deserves more attention, particularly by the internist, than it generally receives. First there is a consideration of the circumstances under which suicide is more likely to occur, insofar as such circumstances can be defined; the points made are illustrated by informative case reports. Then follows an illuminating discussion of motivating forces, and how these can be recognized by the sensitive physician. And finally, the crux of the problem, know thy patient, not only his serum electrolyte level.

Reviews

The Long Term Management of Hepatolenticular Degeneration (Wilson's Disease)
I. HERBERT SCHEINBERG AND IRMIN STERNLIEB 316

This is a sober evaluation of currently available methods of prevention and treatment of Wilson's disease, and also a contribution to knowledge of the natural history of the untreated as well as treated disorder. Six patients (one a youngster with as yet latent disease) are described over prolonged periods of observation. Therapy was designed to minimize intake and absorption of copper, and also to promote the excretion of copper from tissue deposits by means of cupriuretic agents, notably penicillamine. (Replacement of ceruloplasmin was tried but proved unsuccessful). The authors graphically describe the difficulties in even the most modern management but perseverance of both patient and physician ultimately won its just awards and, although modestly stated, the results obtained are impressive.

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Central Nervous System Syndromes of "Viral" Etiology. A Study of 713 Cases
HARRY M. MEYER, JR., RICHARD T. JOHNSON, IRVING P. CRAWFORD, HARRY E. DASCOMB AND NANCY G. ROGERS 334

A very large experience (713 cases) in establishing the etiology of aseptic meningitis, encephalitis and paralytic disease of viral origin is reviewed in this paper. A specific etiology could be established in 73 per cent of cases (almost three times the percentage possible in similar case material only a decade ago), implicating forty immunologically distinct infectious agents, chiefly viruses. Certain correlations between infective agent and clinical manifestations, apparent from this study, are helpful in provisional diagnosis. Thus the characteristic acute febrile course, without sequel, of aseptic meningitis (60 per cent of the total cases) was almost invariably due to Coxsackie B, ECHO, mumps, lymphocytic choriomeningitis or poliomyelitis virus, or to leptospirosis. The more severe and protracted course of encephalitis, with not infrequent sequelae or death, was usually associated with mumps, arthropod-borne, herpes simplex or lymphocytic choriomeningitis virus or with tuberculosis. Paralytic disease was, as expected, almost exclusively a sequel of infection with poliomyelitis virus.

Clinicopathologic Conference

Pulmonary Disease and Rapidly Progressive Renal Failure 348
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Case Reports

Lethal Congenital Neutropenia with Eosinophilia Occurring in Two Siblings
JAMES P. ANDREWS, JAMES T. MCCLELLAN AND CARL H. SCOTT 358

The findings and able discussion suggest that this may indeed be a hitherto undifferentiated syndrome.

Pathological Calcification of the Lungs Following Intravenous Administration of Calcium . . . . . C. ROBERT COOKE AND JOHN W. HYLAND 363

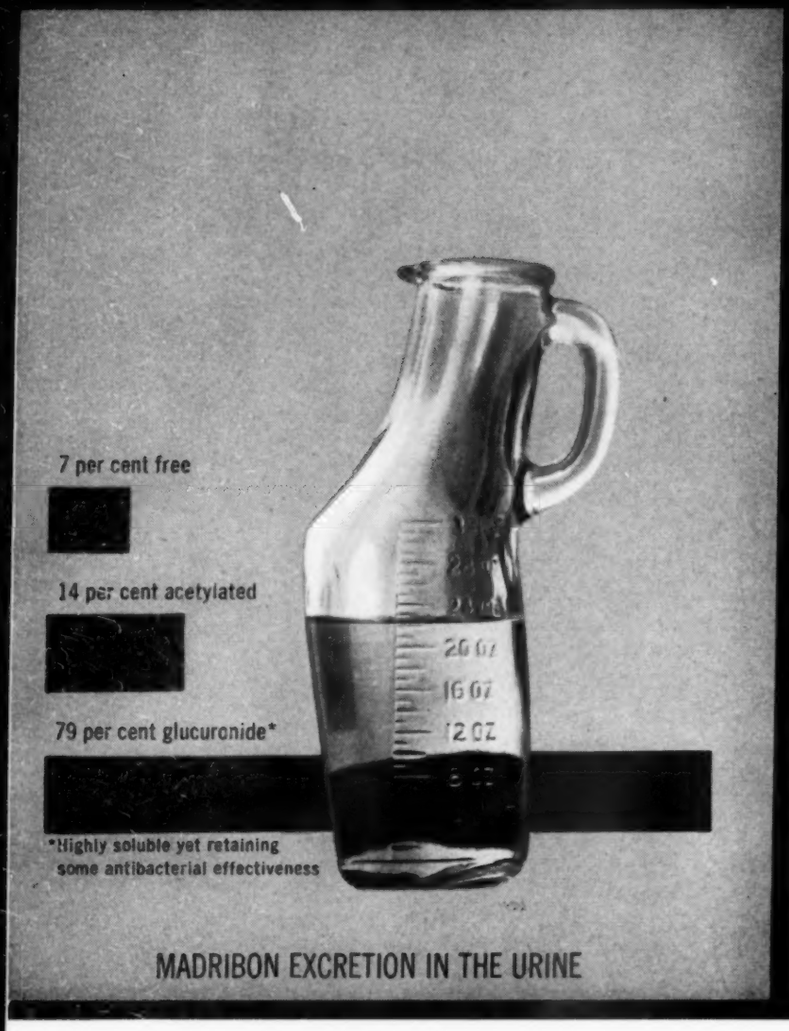
A most unusual case.

Metabolic Observations in Adult Hypophosphatasia
MAJ. WILLIAM R. BEISEL, CAPT. K. FRANK AUSTEN, HYMAN ROSEN AND LT. COL. E. G. HERNDON, JR. 369

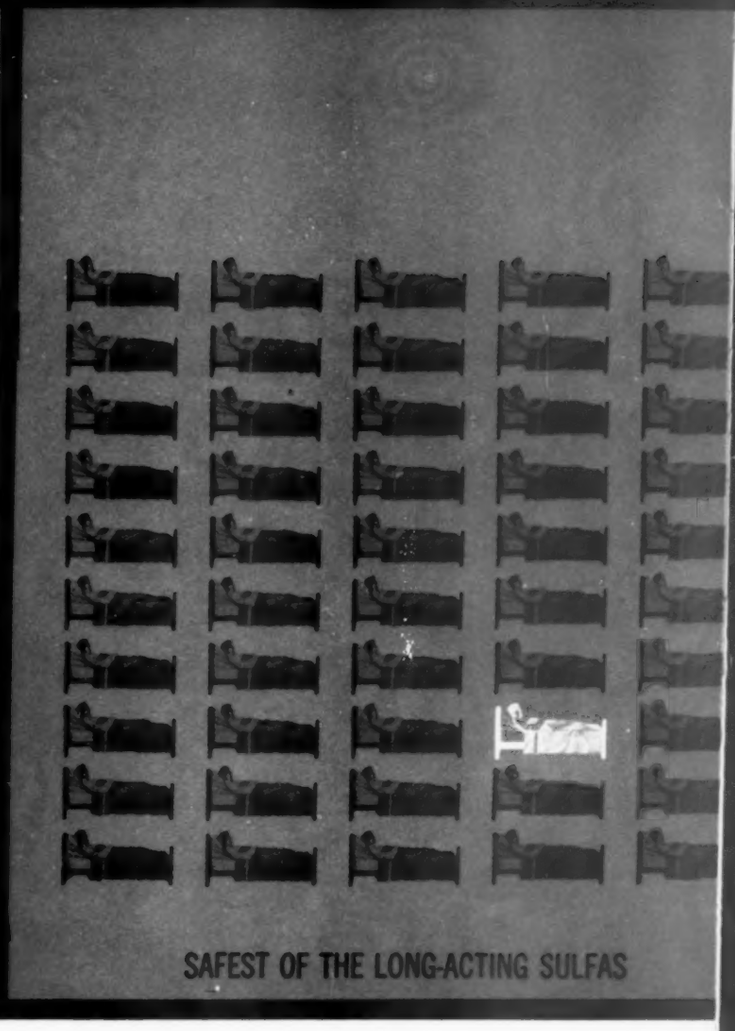
Unless searched for, hypophosphatasia is apt to escape diagnosis in the adult; it was recognized by chemical studies in the case reported, despite scanty clinical and roentgenographic manifestations.

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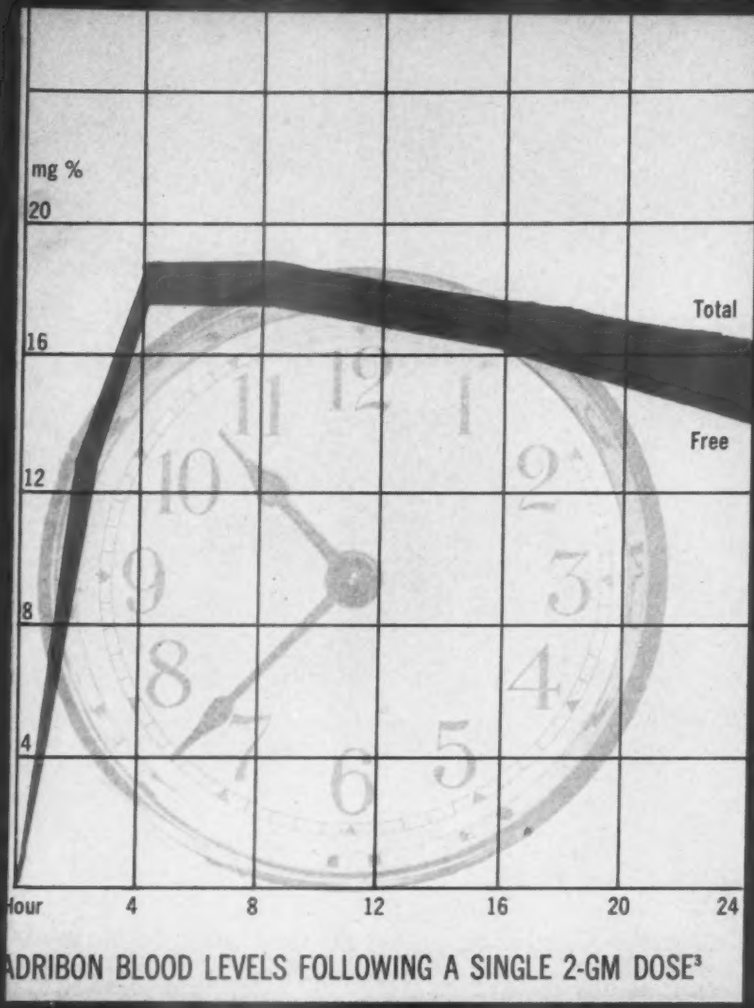
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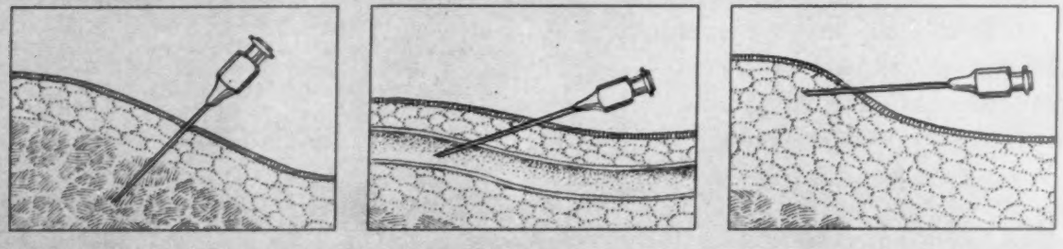
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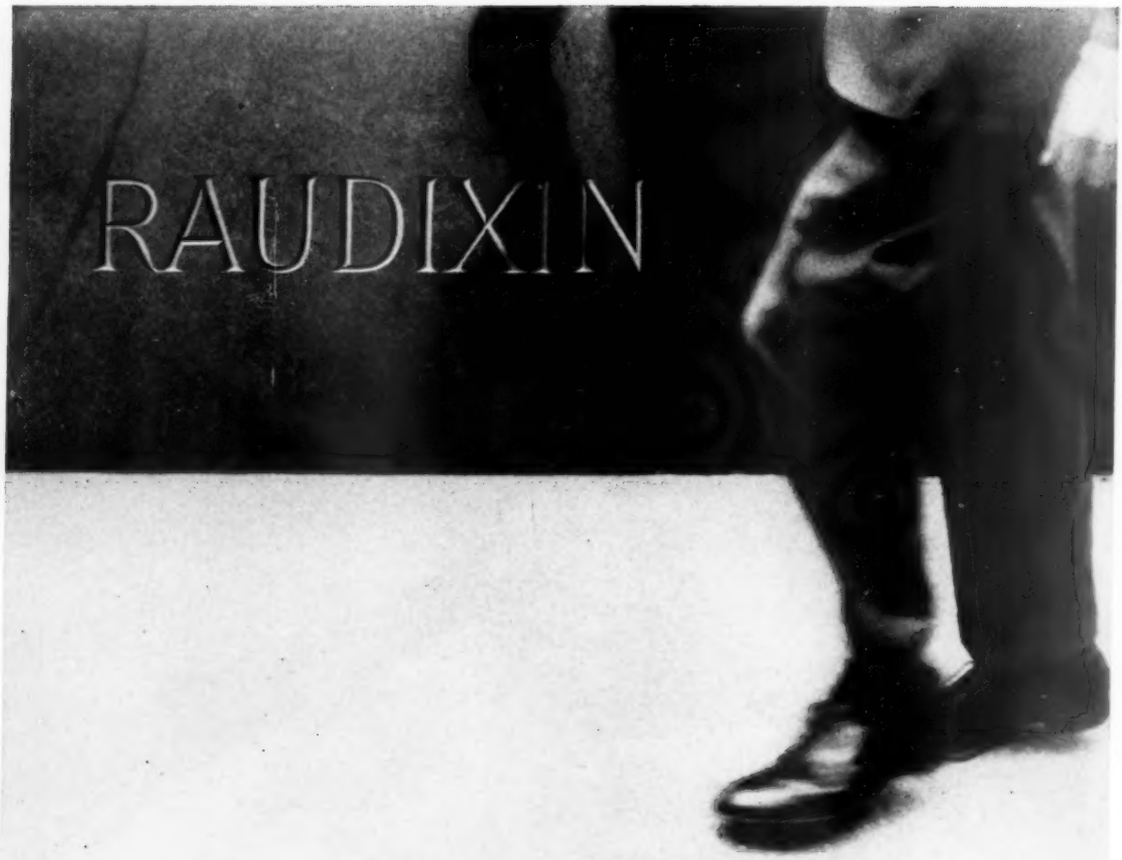
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1. Blumberg, N. *et al.*: Fed. Proc. 17:351, March 1958. **2.** Boyd, L. J. *et al.*: Am. J. Cardiol. 3:229, Feb. 1959. **3.** Brick, H. *et al.*: J. Social Therapy 4:190, 1958. **4.** Bulla, J. D. *et al.*: Am. Pract. & Digest Treat. 10:1961, Nov. 1959. **5.** Ewing, J. A. and Haizlip, T. M.: Am. J. Psychiat. 114:835, March 1958. **6.** Friedman, A. P.: Ann. N. Y. Acad. Sc. 67:822, May 9, 1957. **7.** Greenberg, L. A. *et al.*: Ann. N. Y. Acad. Sc. 67:816, May 9, 1957. **8.** Holliday, A. R.: Northwest Med. 58:837, June 1959. **9.** Hollister, L. E. *et al.*: Dis. Nerv. System 17:289, Sept. 1956. **10.** Laird, D. M. *et al.*: Dis Nerv. System 18:346, Sept. 1957.

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11. Lasagna, L.: J. Chron. Dis. 3:122, Feb. 1956. **12.** Muhlfelder, W. J. *et al.*: Dis. Nerv. System 20:587, Dec. 1959. **13.** Pollak, M.: Practitioner 184:231, Feb. 1960. **14.** Rickels, K. *et al.*: J.A.M.A. 171:1649, Nov. 21, 1959. **15.** Russek, H. I.: Am. J. Cardiol. 3:547, April 1959. **16.** Tucker, K. and Wilensky, H.: Am. J. Psychiat. 113:698, Feb. 1957.

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THE PRESENT STATUS OF ORAL PENICILLIN

1
2
3
4
5
6



A Comparison of Potassium Penicillin V and Synthetic Penicillin

1 *On antibacterial activity in the serum*

In a recent study, Griffith[1] undertook to compare the antibacterial activity of three oral penicillins.

Included were forms of potassium penicillin V and G and alpha-phenoxyethyl penicillin. Typical crossover procedures were used, and results were measured by the tube dilution technique.

When potassium penicillin V was compared directly with the synthetic form, Griffith found that the former not only produced peak levels of activity faster, but in values almost half again as high as those registered with the synthetic. He wrote: "Measuring antibacterial activity in the sera using the serial tube dilution method and a pathogen as the indicator organism is more informative regarding relative antibacterial effectiveness than reporting 'blood levels' in micrograms."

2 *Greater activity of potassium penicillin V confirmed*

A direct laboratory comparison[2] of the two penicillins revealed a measurable difference in antibacterial activity. In the following chart, these values are interpreted in terms of reciprocal of the dilution inhibiting growth.

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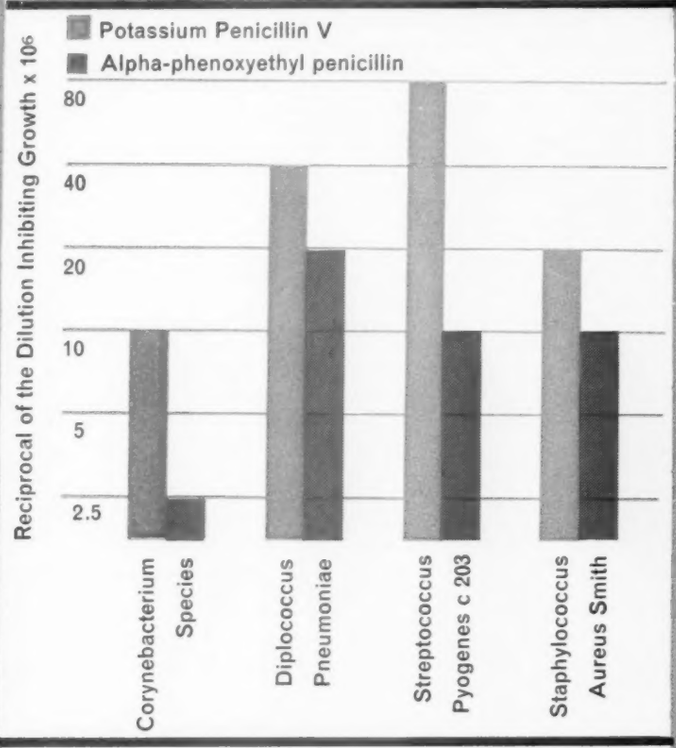
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offers greater antibacterial activity
against penicillin-sensitive organisms

In Vitro Activity of Penicillin V and Alpha-Phenoxyethyl Penicillin

Note, that against four common disease-producing organisms, potassium penicillin V gives from two to eight times more antibacterial activity than alpha-phenoxyethyl penicillin.



3 *On high blood levels*

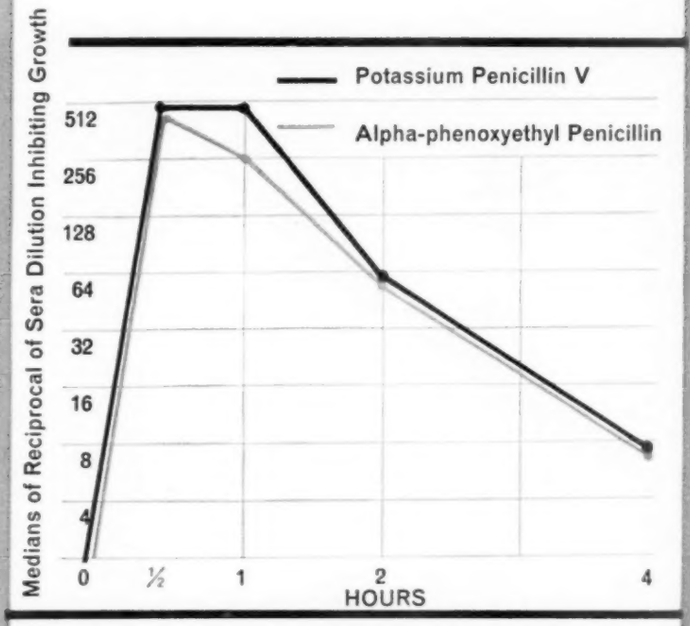
A number of investigators have demonstrated serum concentrations in the same range following equivalent doses of potassium penicillin V and alpha-phenoxyethyl penicillin.

McCarthy, et al.,[3] after investigating the two penicillins, reported: "These crossover studies indicate that the new synthetic penicillin and penicillin V are absorbed in a remarkably similar manner and degree and that these forms of penicillin yield quite comparable serum levels when given in the same manner to the same individuals at different times."

At Abbott Laboratories, scientists[2] found after their study that antibacterial activity in the sera of human subjects given equivalent doses of penicillin V or synthetic penicillin showed no significant differences between the two penicillins.

Comparative Serum Antibacterial Activity Study of Potassium Penicillin V and Alpha-phenoxyethyl Penicillin

Doses of 250 mg. (400,000 units) were given to 30 human subjects. The study revealed little difference in serum antibacterial activity between the two penicillins.



In England, where synthetic penicillin was first discovered and marketed, the Journal of the British Medical Association (after studying a commercial brochure) stated: "There is no evidence here of any activity superior to that of other penicillins against Gram-negative species, and what differences there are against sensitive species are in favour of penicillin G or V or both; this applies to all varieties of streptococci tested.[4]"

4 *On resistance to penicillinase*

In comment on this phase of the new penicillin, McCarthy stated[3]: "Both of these penicillins are qualitatively similar to penicillin G in their susceptibility to penicillinase produced by *Staphylococcus aureus.*"

In further comment on this problem, he said: "Other observations not detailed here have indicated some differences in susceptibility of a number of strains of staphylococci to these 2 forms of penicillin and to penicillin G, but these differences, too, are not large enough to be of clinical importance..."

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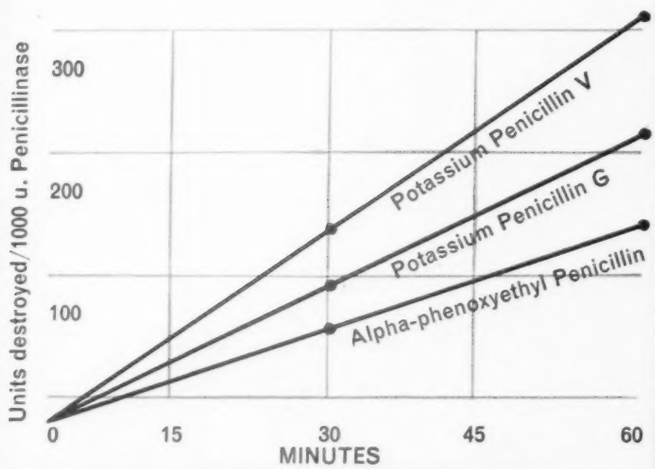
(Potassium Penicillin V)

offers greater antibacterial activity
against penicillin-sensitive organisms

At Abbott, investigators studying the same subject[2] found that synthetic penicillin is destroyed by penicillinase at a rate approximately ⅔ that of penicillin G and ½ that of penicillin V.

Sensitivity to Penicillinase

Note that the rate of destruction of all three penicillins is so great that the differences have no therapeutic significance.



Additional studies by the same scientists[2] indicated that both synthetic penicillin and penicillin V were relatively inactive against several penicillinase-producing staphylococci. (See chart below).

Comparative Activity of Potassium Penicillin V and Alpha-phenoxyethyl Penicillin Against Penicillinase-Producing Staphylococci

Note that although synthetic penicillin is slightly more active, the concentration required to inhibit growth is greatly in excess of an obtainable therapeutic level, and therefore of little therapeutic significance.

Strain	M.I.C., mcg./ml.	
	Penicillin V	Synthetic Penicillin
Wise J155	> 800	> 800
Wise J306	300	75
W. E. B.	> 800	> 800
Wise J628	> 400	> 400
Treaster	> 800	800
Gill 1322	> 800	> 800

COMPOCILLIN®-VK

(Potassium Penicillin V)

offers greater antibacterial activity
against penicillin-sensitive organisms

5 *On the comparative safety of oral penicillin*

In 1957, a nationwide survey[5] of antibiotic reactions was made. One of the conclusions reached by the investigators in regard to penicillin reactions was, "It is clear also that the oral route is the much safer method of administration, both from the standpoint of numbers of reactions and of mortality." There is no evidence to show that any form of oral penicillin is less allergenic than another oral form.

6 *On the advantages of Compocillin-VK*

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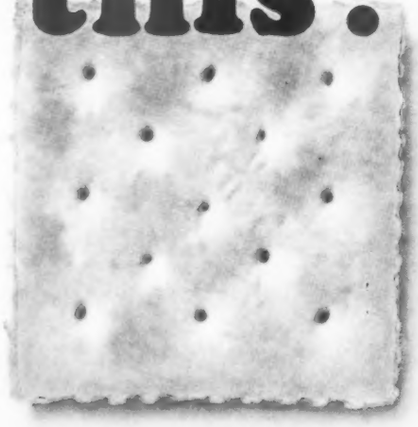
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SIDE REACTIONS AS FEW AS PLACEBO / NEW ENGLAND J. MED. 261:478, 1959 (Schiller, I. W., and Lowell, F. C.) "In contrast to the frequency of central-nervous-system-stimulating or sedative effects produced by chlorprophenpyridamine was the virtual freedom from these relatively disagreeable effects. ...Side effects in patients taking placebo were as frequent as those seen with parabromdylamine (Dimetane)."

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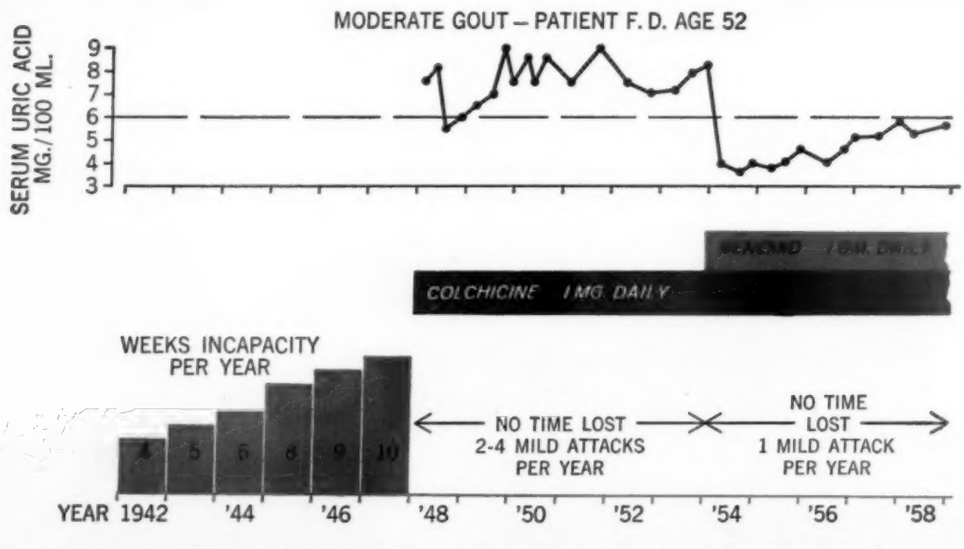
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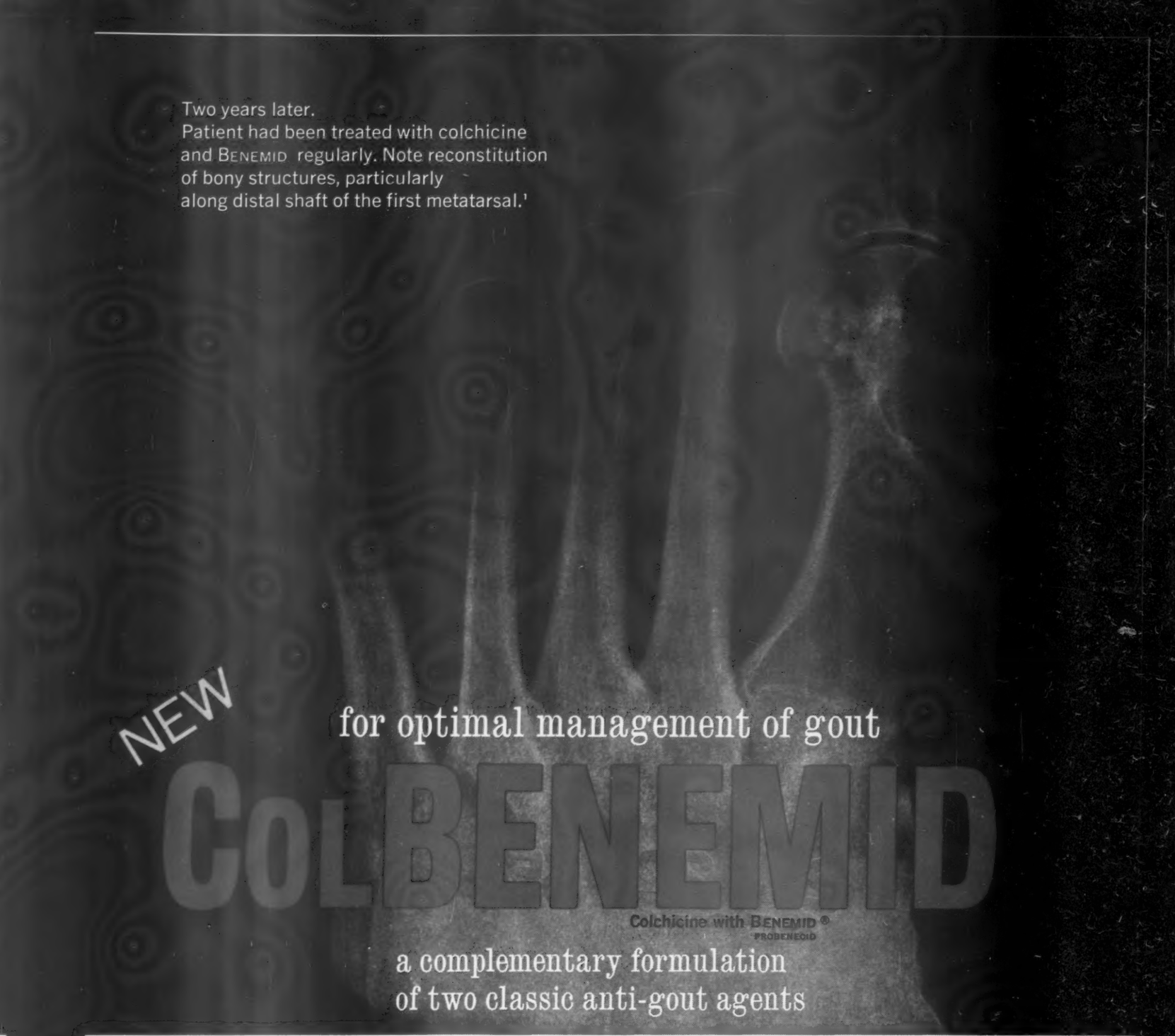
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1. Talbott, J. H.: Gout, New York, Grune & Stratton, 1957, pp. 162, 163. 2. Talbott, J. H.: Gouty arthritis, Minn. Med. *42*:1044, Aug. 1959. 3. Talbott, J. H.: Recognition and treatment of gouty arthritis, Current Medical Digest *26*:57, Nov. 1959.

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"All three of the patients with Laennec's cirrhosis, ascites and edema had a favorable response, with a mean weight loss of 8 lbs., during the five-day treatment period with a slight decrease in edema." Castle, C. N., Conrad, J. K. and Hecht, H. H.: Arch. Int. Med., **103**:415, (March) 1959.



in renal edema

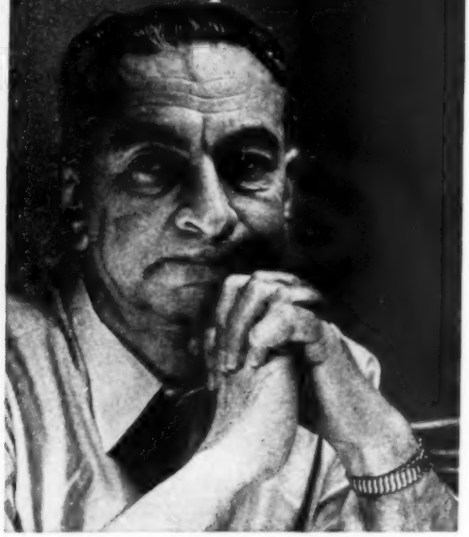
"In a study of 10 patients with the nephrotic syndrome associated with various types of renal disease, orally administered chlorothiazide was a successful, and sometimes dramatic, diuretic agent." Burch, G. E. and White, M. A., Jr.: Arch. Int. Med., **103**:369, (March) 1959.

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VISTARIL®

hydroxyzine pamoate

relieves associated anxiety in the cardiac patient



IN BRIEF

VISTARIL gently calms the fears of the cardiac patient. It permits the patient to remain calm but alert, because it is not a cortical depressant. An ideal adjunct in the treatment of heart disease, it may be used concurrently with digitalis or other medications.

INDICATIONS: VISTARIL is a rapid-acting tranquilizer with a wide margin of safety. It is effective in the symptomatic treatment of a variety of neuroses and other emotional disturbances manifested by anxiety, apprehension or fear — whether occurring alone or complicating a physical illness.

ADMINISTRATION & DOSAGE: VISTARIL dosage varies with individual requirements and ranges from 25 mg. t.i.d. to 100 mg. q.i.d. for adults. The usual dosage for children *under* 6 years is 50 mg. daily in divided doses; children *over* 6 years — 50 to 100 mg. in divided doses. For parenteral dosage information consult package insert.

SIDE EFFECTS: Drowsiness may occur in some patients; if so, it is usually transitory, disappearing within a few days of continued therapy or upon reduction of dosage. Dryness of mouth may be encountered at higher doses.

PRECAUTIONS: The potentiating action of hydroxyzine is mild, but must be taken into consideration when the drug is used in conjunction with central nervous system depressants.

SUPPLY: *Capsules* — 25, 50, and 100 mg. *Oral Suspension* — 25 mg. per 5 cc. teaspoonful. *Parenteral Solution* (as the HCl) — 10 cc. vials and 2 cc. Steraject® Cartridges, 25 mg. per cc.; 2 cc. ampules, 50 mg. per cc.

Detailed professional information is available on request from Pfizer Laboratories Medical Department.

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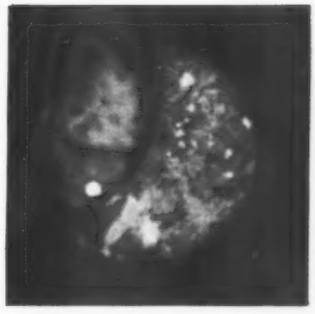
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The Upjohn Company, Kalamazoo, Michigan

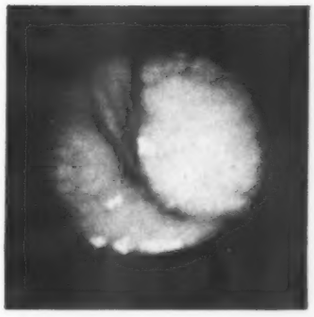
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Excellent results in ulcerative colitis even where other steroids have failed

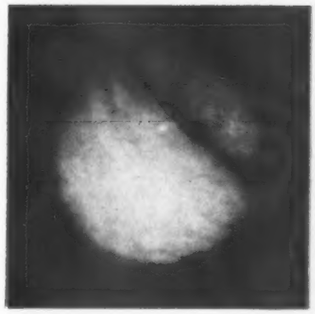
Proctoscopic view of the sigmoid in acute stage of ulcerative colitis



Proctoscopic view of the sigmoid following Depo-Medrol retention enemas for acute stage of ulcerative colitis



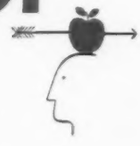
Proctoscopic view of sigmoid colon in a normal person



In controlling ulcerative colitis (recurrent, moderately severe, severe, and resistant), Depo-Medrol† can be given topically (by enema or rectal instillation) in requisitely large doses without producing significant side effects. Excellent results are obtainable even where other steroids have failed and improvement continues on oral Medrol maintenance dosage.

there is only one methylprednisolone, and that is

Medrol*

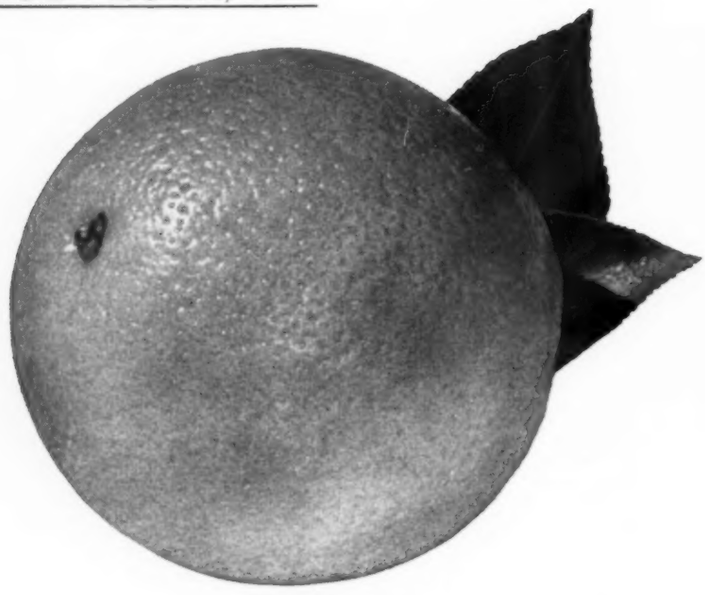


the corticosteroid that hits the disease, but spares the patient

Medrol is supplied as 4 mg. tablets in bottles of 30, 100 and 500; as 2 mg. tablets in bottles of 30 and 100; and as 16 mg. tablets in bottles of 50. Depo-Medrol is supplied as 40 mg. per cc. injectable suspension in 1 cc. and 5 cc. vials. Mode of administration: Depo-Medrol (40-120 mg.) given as retention enema or by continuous drip three to seven times weekly.

*Trademark, Reg. U. S. Pat. Off.—methylprednisolone, Upjohn
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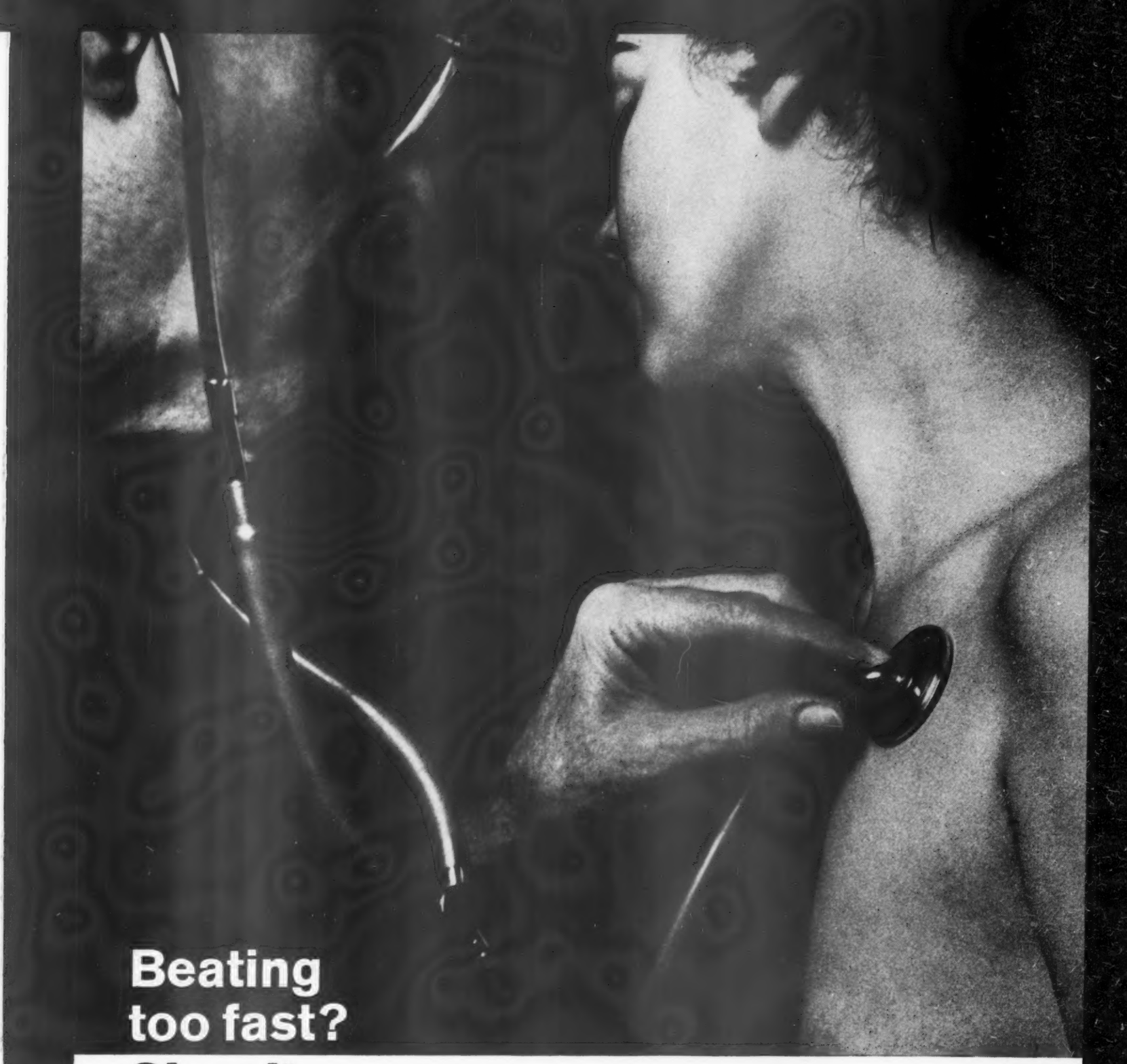
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Exchange Brand Citrus Pectin and pectin derivatives widely used in therapeutic specialties include:

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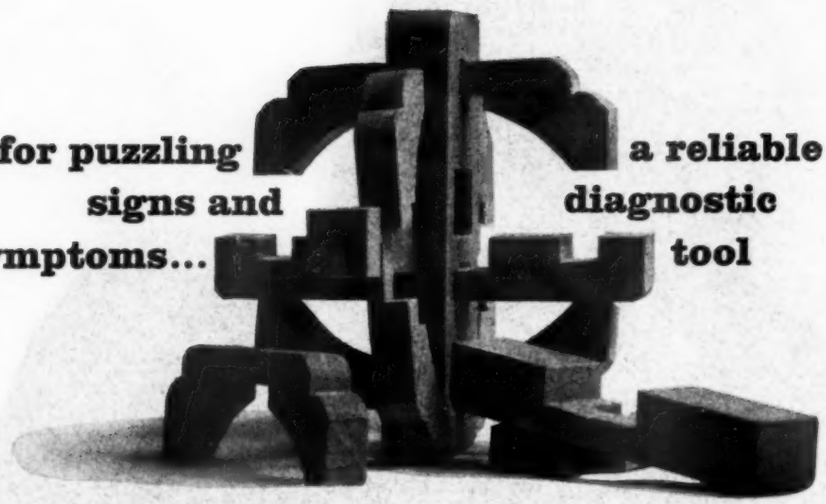
Serpasil has proved effective as a heart-slowing agent in the following conditions: mitral disease; myocardial infarction; cardiac arrhythmias; neurocirculatory asthenia; thyroid toxicosis; excitement and effort syndromes; cardiac neurosis; congestive failure. Serpasil should be used with caution in patients receiving digitalis and quinidine. It is not indicated in cases of aortic insufficiency.

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References: 1. Editorial: J.A.M.A. 160:672 (Feb. 25) 1956. 2. Levinger, G. L.; Levy, H., and Elster, S. K.: Ann. Int. Med. 46:68, 1957. 3. Kroop, I. G., and Shackman, N. H.: Am. J. Med. 22:90, 1957. 4. Kroop, I. G., and Shackman, N. H.: Proc. Soc. Exper. Biol. & Med. 86:95, 1954. 5. Shubin, H.; Glaskin, A., and Heiken, C. A.: Tuberc. 15:62, 1955. 6. Losner, S., and Volk, B. W.: New York J. Med. 56:2665 (Sept. 1) 1956. 7. Roantree, R. J., and Rantz, L. A.: A.M.A. Arch. Int. Med. 96:674, 1955. 8. Goldner, F., and Meador, C.: South M. J. 48:1339, 1955. 9. Hedlund, P.: Acta med. scandinav. supp. 196:579, 1947. 10. Shackman, N. H.; Heffer, E. T., and Kroop, I. G.: Am. Heart J. 48:599 (Oct. 13) 1954. 11. Boland, E. W.: California Med. 82:65, 1955. 12. Knights, E. M., Jr.; Hutchins, M.; Morgan, E., and Ploompuu, J.: J.A.M.A. 162:9 (Sept. 1) 1956. 13. Shetlar, M. R.; Bullock, J. A.; Shetlar, C. L., and Payne, R. W.: Proc. Soc. Exper. Biol. & Med. 88:107, 1955. 14. Ruggieri, P. A.: J. M. Soc. New Jersey 52:500, 1955. 15. Dodd, K.: Mississippi Doctor 33:59, 1955.

Complete literature and bibliography available on request.

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adequate nutrition in 900-calorie program

One-half pound of Metrecal powder, the daily 900-calorie feeding, provides 70 grams of high-grade protein plus vitamins and minerals to meet or exceed all established minimum daily requirements. Metrecal itself *is* the diet—the *complete* diet.

impressive clinical results

in uncomplicated overweight: In a twelve-day study of 100 patients[1] on the Metrecal 900-calorie program, the average total weight loss per subject was 6½ pounds (over ½ pound a day). In another study,[2] patients on the 900-calorie Metrecal program for two to thirty weeks showed a weight loss per patient of 3 to 5 pounds weekly during the initial weeks and 2 to 2½ pounds per patient per week thereafter.

in overweight complicated by illness: In a study of 42 overweight patients,[3] some with serious medical disorders such as arthritis, cardiovascular disease, diabetes mellitus and gout, the 900-calorie daily Metrecal program provided an average total weight loss of 6.3 pounds per patient during the first week. The investigator encountered no significant complications in the management of these patients.

excellent patient cooperation

All investigators[1,2,3] commented on excellent patient cooperation. This was attributed to the effective loss of weight, the satiety of Metrecal which satisfied hunger in a majority of patients, its simplicity of use—no calorie counting or menu planning required—and its palatability. No appetite depressants were required.

flexibility in use

When more than 900 calories are permitted, either the daily allotment of ½ pound of Metrecal may be increased or it may be used in conjunction with low-calorie foods. Metrecal may also be used for one or two meals a day or as the total diet two or three days a week.

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All patients do to make a full day's supply of Metrecal beverage is mix ½ pound of Metrecal powder with a quart of water. Or they may make a glassful at a time. For variety, Metrecal is available in Plain, Chocolate or Butterscotch flavors.

Weight-Control Guide for patient instruction is available from your Mead Johnson representative, or by writing to us, Evansville 21, Indiana.

references. (1) Antos, R. J.: Southwestern Med. *40*:695-697 (Nov.) 1959. (2) Tullis, I. F.: Initial Experience with a Simple Weight Control Formula, to be published. (3) Roberts, H. J.: Effective Long-Term Weight-Reduction—A Therapeutic Breakthrough, to be published.

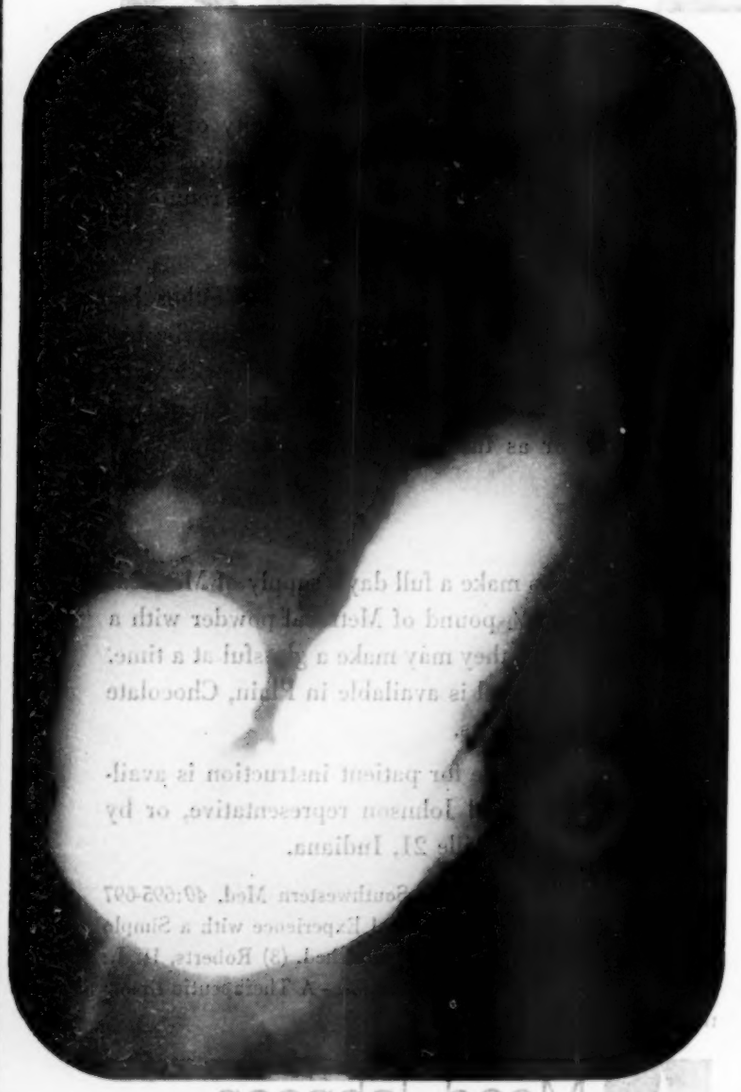


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Symbol of service in medicine

EFFECTIVENESS OF "MUREL"-S. A. IN SPASM VISUALLY CONFIRMED

55 year old male with symptoms of partial obstruction of the stomach; nausea and vomiting.



March 1st, 1960: Large dilated stomach with incomplete pyloric obstruction. Etiology undetermined.

Patient placed on "Murel"-S.A. — 2 tablets b.i.d. for one week — plus bland diet. No other medication.



March 10th, 1960: Stomach of normal size and tone. Large ulcer crater now visualized in the region of previously noted pyloric spasm and incomplete filling.

Medical Records of Ayerst Laboratories

in G.I., G.U. and Biliary SPASM

"Murel"-S.A.

Sustained Action Tablets

prompt, continuous and prolonged antispasmodic action for 6 to 9 hours with a single tablet

"MUREL" Advantages[1-4]

- Exceptionally effective clinically because three-way mechanism of action in one molecule (anticholinergic, musculotropic, ganglion-blocking) exerts synergistic spasmolytic effect
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Suggested Average Dosage: 40 to 80 mg. daily, depending on condition and severity. The higher range of dosage is usually required in spasm of the genitourinary and biliary tracts. One "Murel"-S.A. Sustained Action Tablet morning and evening. *When anxiety and tension are present,* "Murel" with Phenobarb-S.A. is suggested.

Available as: No. 315—"Murel"-S.A., 40 mg. Valethamate bromide; and No. 319—"Murel" with Phenobarb-S.A., with ½ gr. phenobarbital, present as the sodium salt. Both in bottles of 100 and 1,000.

Also available: "Murel" Tablets No. 314—10 mg. Valethamate bromide; "Murel" with Phenobarbital Tablets No. 318—10 mg. Valethamate bromide and ¼ gr. phenobarbital.

"Murel" Injectable No. 405—10 mg. Valethamate bromide per cc.

Precautions: As with other antispasmodic agents, caution should be exercised in patients with prostatic hypertrophy, glaucoma, and in the presence of cardiac arrhythmias.

References available on request.

Ayerst® *AYERST LABORATORIES* New York 16, N.Y. • Montreal, Canada

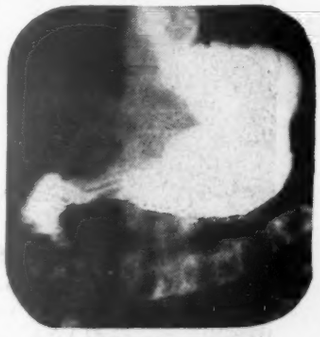
for acute, severe episodes
"MUREL" Injectable

Female patient, age 55, complaining of nausea and epigastric discomfort after meals.

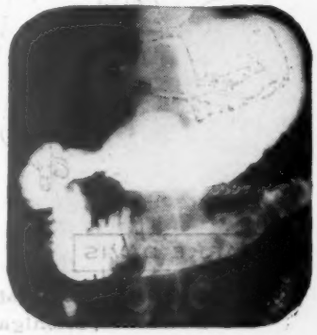
Diagnosis: Hiatus hernia and gastric ulcer.



1 hour after barium administration: Retention of barium due to spasticity of the gastric outlet, and incomplete visualization of the pylorus, duodenum and duodenal sweep. (Some barium has entered the small bowel.)



20 minutes after administration of "Murel" 2 cc. I.V.: Barium entering duodenum and duodenal sweep as spasticity is relieved.



10 minutes later: Good filling of the gastric outlet as well as of the duodenal sweep.

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- No barbiturate depression
- No suppression of adrenal function

Each tablespoonful (15 cc.) contains theophylline 80 mg. (equivalent to 100 mg. aminophylline) in a hydroalcoholic vehicle (alcohol 20%).

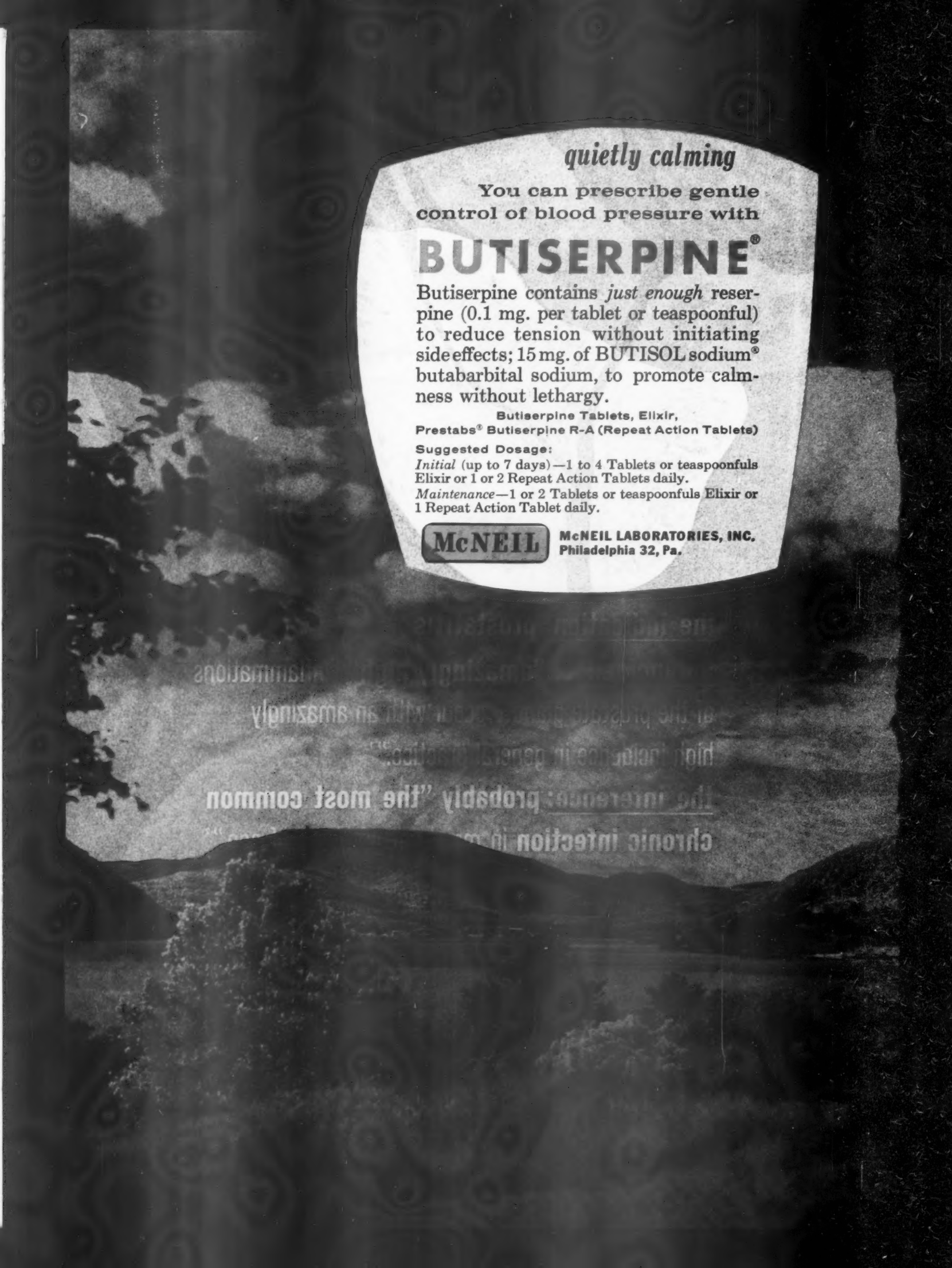
For acute attacks: Single dose of 75 cc. for adults; 0.5 cc. per lb. of body weight for children.

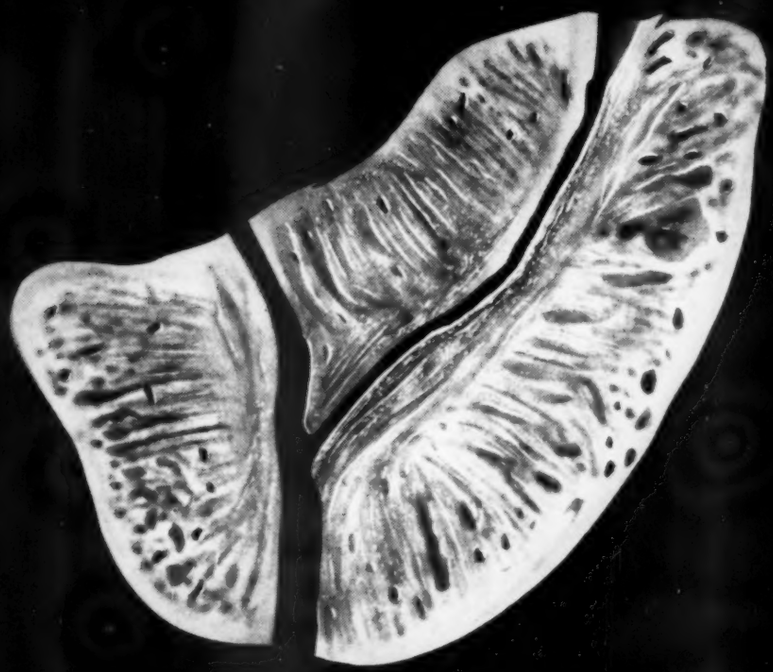
For 24 hour control: For adults 45 cc. doses before breakfast, at 3 P.M., and before retiring; after two days, 30 cc. doses. Children, 1st 6 doses 0.3 cc.—then 0.2 cc. (per lb. of body weight) as above.

1. Schluger, J. et al.: Am. J. Med. Sci. 233:296, 1957.
2. Bradwell, E. K.: Acta med. scand. 146:123, 1953.
3. Truitt, E. B. et al.: J. Pharm. Exp. Ther. 100:309, 1950.

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Butiserpine contains *just enough* reserpine (0.1 mg. per tablet or teaspoonful) to reduce tension without initiating side effects; 15 mg. of BUTISOL sodium® butabarbital sodium, to promote calmness without lethargy.
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the indication: prostatitis

the incidence: "amazingly high"—"Inflammations of the prostate gland...occur with an amazingly high incidence in general practice."[1]

the inference: probably "the most common chronic infection in men over 40 years of age."[2]

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". . . by far the most effective drug to be employed, and this has been substantiated in practice. It is a drug of low toxicity and, what is more important, bacteria rarely if ever become resistant to it. It can be employed for long periods of time, is bactericidal and does not favor the appearance of monilial infections."[3]

In acute prostatitis: "Antibacterial medication, preferably FURADANTIN (Eaton) 100 mg. 4 times daily is indicated . . ."[4]

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In benign prostatic hypertrophy (to prevent or treat concomitant infection): "Nitrofurantoin [FURANDANTIN] may be used for protracted periods for the suppression of infection in the urinary tract, even in the presence of probable obstruction . . . it may provide prolonged relief from symptoms and permit better selection of the proper time for surgical or manipulative procedures."[6]

Postoperatively in prostatic surgery: "In conjunction with routine postoperative care, FURADANTIN is frequently used."[7]

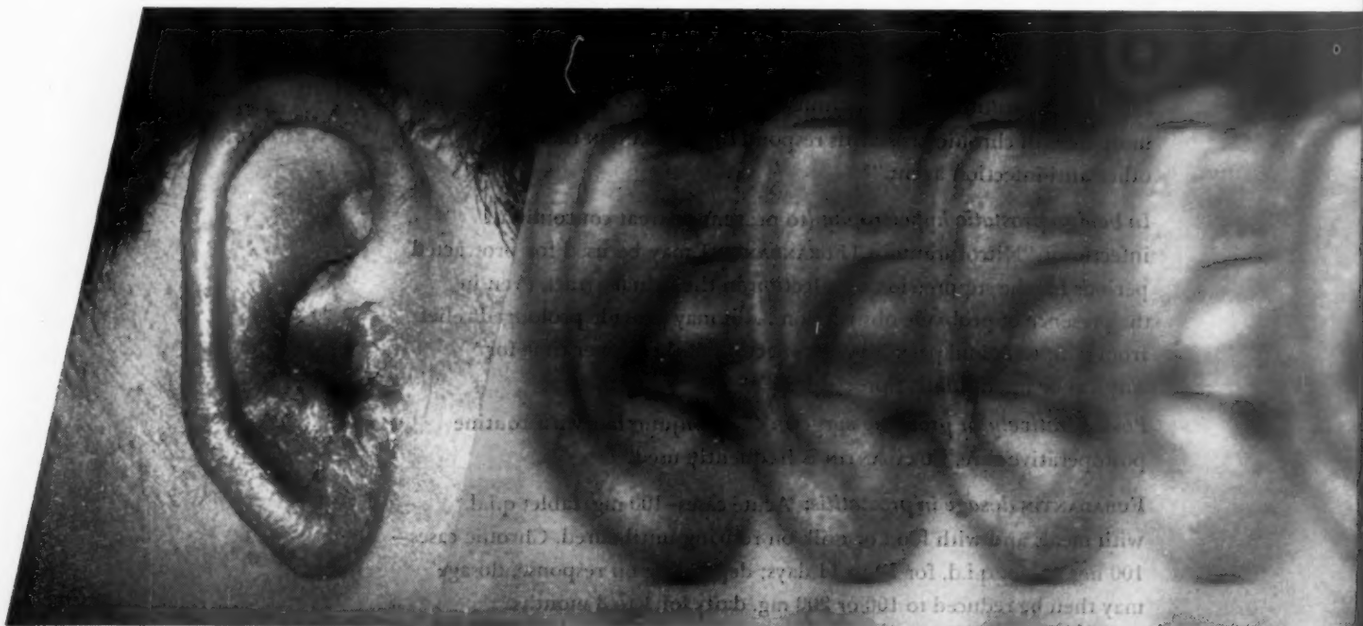
FURADANTIN ***dosage in prostatitis:*** Acute cases—100 mg. tablet q.i.d. with meals and with food or milk on retiring until cured. Chronic cases—100 mg. tablet q.i.d. for 10 to 14 days; depending on response, dosage may then be reduced to 100 or 200 mg. daily for 1 to 3 months.

Supplied: Tablets, 50 and 100 mg., Oral Suspension, 25 mg. per 5 cc. tsp.

References: 1. Campbell, M. F.: Principles of Urology, Philadelphia, W. B. Saunders Co., 1957. 2. Farman, F., and McDonald, D. F.: Brit. J. Urol. **31**:176, 1959. 3. Sanjurjo, L. A.: Med. Clin. N. America **43**:1601, 1959. 4. Barnes, R. W.: Prostatitis, *In* Conn, F.: Current Therapy 1957, Philadelphia, W. B. Saunders Co., 1957. 5. Barnes, R. W., in discussion of Chinn, J., and Bischoff, A. J.: Tr. West. Sect. Am. Urol. Ass. **22**:189, 1955. 6. Jawetz, E.: A.M.A. Arch. Int. M. **100**:549, 1957. 7. Glazier, M., and Lombardo, L. J., Jr.: From the film *Retropubic Prostatovesiculectomy*, Eaton Laboratories, Norwich, N. Y., 1959.

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Nighttime gastric secretion hits its peak between 2 and 4 a.m. And that's just when Tral 75 mg. Gradumet, taken at bedtime, is releasing most of its anticholinergic. The patient gets most of the medication when he needs it most . . . in the middle of the night. • Thereafter, Tral 75 mg. Gradumet keeps right on working until the patient wakens the next morning, after a refreshing sleep. And since acidity is controlled the night through, the ulcer has a better chance to heal. • Gradumet's built-in timing is dependable, too . . . never affected by coating thickness, pH or other variables. • In bottles of 50 and 500.

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. . . and when the problem is functional bowel disorder specify new Filmtab®

TRALCYON™

each Filmtab offers 25 mg. Tral plus 300 mg. ectylurea

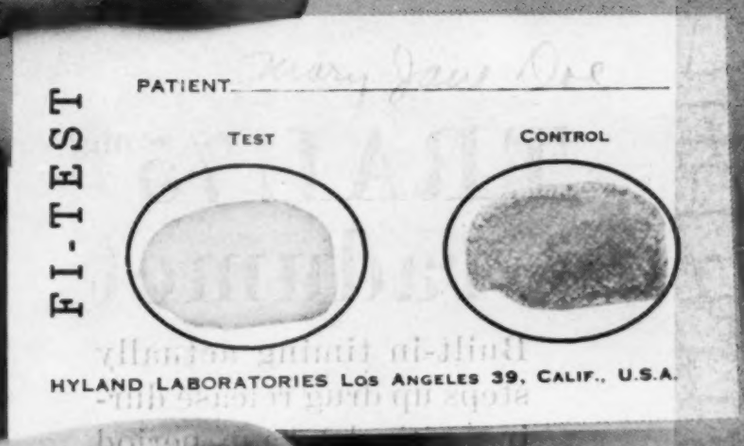
® Tral Gradumet — Hexocyclium Methylsulfate in Long-Release Dose Form*, Abbott. *Patent applied for. ®Filmtab—Film-sealed tablets, Abbott.

002207

NEW

RAPID SCREENING TEST FOR

HYPOFIBRINOGENEMIA



FI-TEST*

Test results at patient's bedside — from skin puncture to reading — in less than 2 minutes. Only one drop of blood required. Test performed by simple, rapid-slide technic.

FI-TEST indicates whether fibrinogen content is above or below 100 mg-%, the concentration considered critical. Easy-to-read results indicate promptly whether or not replacement fibrinogen is needed. (If reading shows a normal fibrinogen level, needless replacement therapy may be avoided and the physician is alerted to seek another explanation for continued bleeding.)

Supplied in compact ready-to-use kits containing complete materials for 6 determinations.



*TRADEMARK OF HYLAND LABORATORIES

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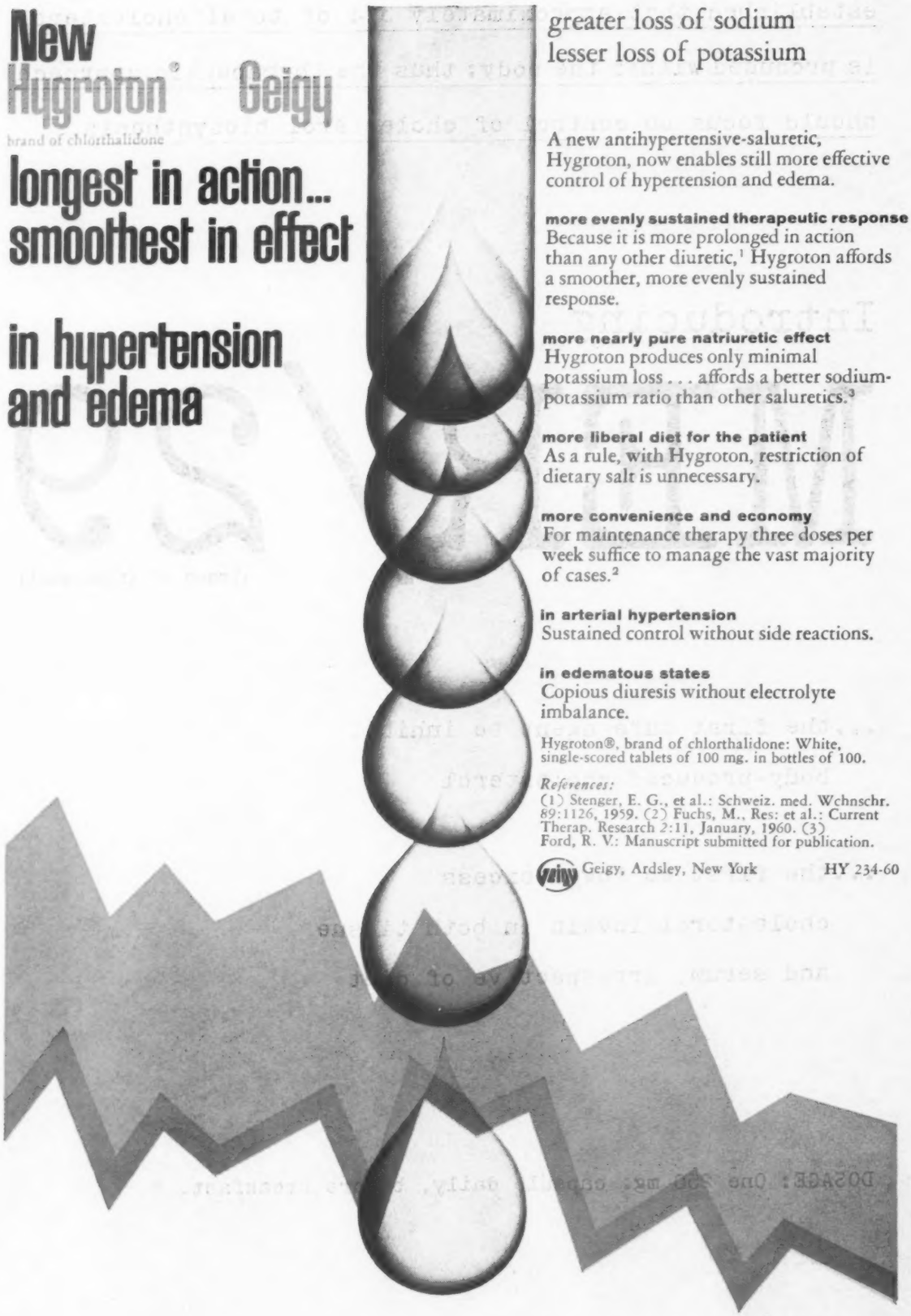
HYLAND LABORATORIES
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160 Lockwood Ave., Yonkers, N.Y.

New Hygroton® Geigy

brand of chlorthalidone

longest in action... smoothest in effect

in hypertension and edema



greater loss of sodium
lesser loss of potassium

A new antihypertensive-saluretic, Hygroton, now enables still more effective control of hypertension and edema.

more evenly sustained therapeutic response
Because it is more prolonged in action than any other diuretic,[1] Hygroton affords a smoother, more evenly sustained response.

more nearly pure natriuretic effect
Hygroton produces only minimal potassium loss . . . affords a better sodium-potassium ratio than other saluretics.[3]

more liberal diet for the patient
As a rule, with Hygroton, restriction of dietary salt is unnecessary.

more convenience and economy
For maintenance therapy three doses per week suffice to manage the vast majority of cases.[2]

in arterial hypertension
Sustained control without side reactions.

in edematous states
Copious diuresis without electrolyte imbalance.

Hygroton®, brand of chlorthalidone: White, single-scored tablets of 100 mg. in bottles of 100.

References:
(1) Stenger, E. G., et al.: Schweiz. med. Wchnschr. 89:1126, 1959. (2) Fuchs, M., Res: et al.: Current Therap. Research 2:11, January, 1960. (3) Ford, R. V.: Manuscript submitted for publication.

Geigy, Ardsley, New York HY 234-60

Current clinical research has established that approximately 3/4 of total cholesterol is produced within the body: thus the therapeutic approach should focus on control of cholesterol biosynthesis.

Introducing

MER/29

(brand of triparanol)

...the first safe agent to inhibit body-produced cholesterol

...the first to lower excess cholesterol levels in both tissue and serum, irrespective of diet

DOSAGE: One 250 mg. capsule daily, before breakfast.

Merrell SINCE 1828

THE WM. S. MERRELL COMPANY
Cincinnati, Ohio / St. Thomas, Ontario

Trademark: 'MER/29'

MER/29[1-41] is not a cholesterol-lowering agent by the usual definition. Usual measures for lowering cholesterol only modify its intake or accelerate its metabolism. Since dietary cholesterol is the minor source of total body cholesterol, results with previous agents have been limited.

MER/29, however, inhibits cholesterol biosynthesis in the liver and other tissues.[1-4] This activity is partial and takes place at a late stage in the synthesis cycle. Sufficient cholesterol remains to fulfill its role as precursor of other necessary biosynthesized substances.

Thus MER/29 is an inhibitor of excess cholesterol production, and reduced cholesterol levels in both serum[3-6] and tissues[2,4,7] is the net result of this activity. Studies of Hollander and Chobanian,[3] and those of Oaks et al.,[6] found that cholesterol levels were lowered irrespective of diet.

In clinical studies[3-6] MER/29 reduced cholesterol, on the average, 48 mg.%, and reduction ranged from 20 to 110 mg.%. Maximum reduction was reached in 5 to 8 weeks.

A report on MER/29 therapy for patients with hypercholesterolemia and its probable associated conditions:

- coronary artery disease (angina pectoris, postmyocardial infarction)
- generalized atherosclerosis

In some instances,[3-6] MER/29 increased exercise tolerance in patients with angina pectoris. Frequency and severity of anginal attacks were reduced, as was nitroglycerine dependence. Abnormal ECG's did not occur in these patients at the previous levels of exercise. Many of them reported improved sense of good health and well-being. Explanation of these clinical benefits is not yet known. Nevertheless, they prompt mounting interest in MER/29 as an important new agent.

It is equally important that MER/29 has been well tolerated and relatively free of toxic effects. Clinical liver damage has not been encountered; however, since the principal site of action of MER/29 is in the liver, periodic hepatic function tests may be desirable until more long-term safety data are available.

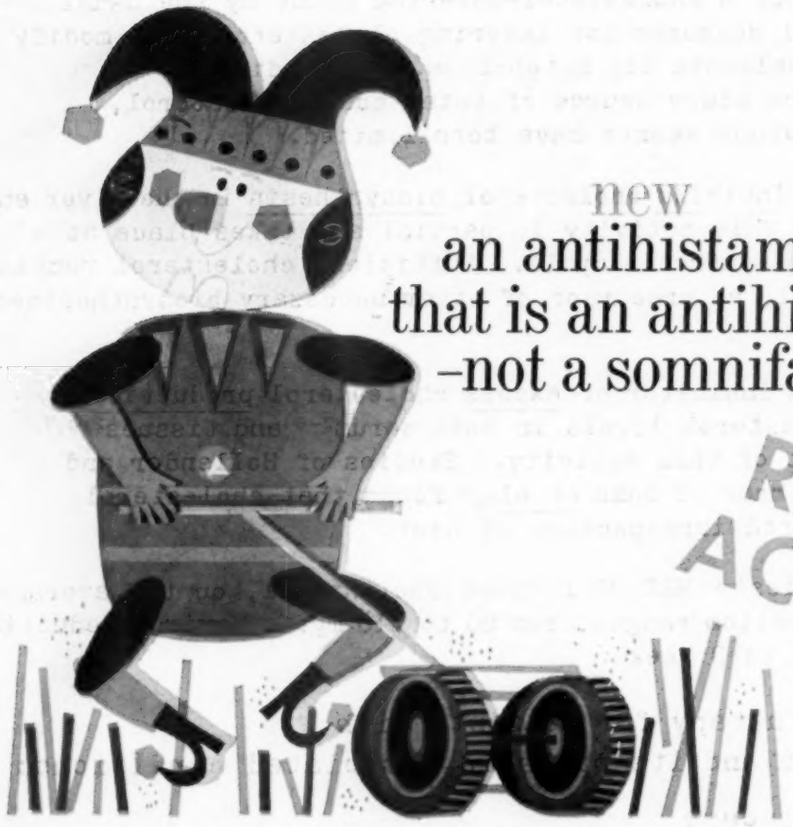
Available: Bottles of 30 pearl gray capsules.

MER/29

1. MacKenzie, R. D., and Blohm, T. R.: Fed. Proc. 18:417, 1959. 2. Blohm, T. R.; Kariya, T., and Laughlin, M. W.: Arch. Biochem. 85:245, 1959. 3. Hollander, W., and Chobanian, A. V.: Boston M. Quart. 10:37, 1959. 4. Kountz, W. B.: Proceedings, Conference on MER/29, Progr. Cardiovasc. Dis. 2:(Suppl.), 541 (May) 1960. 5. Oaks, W., and Lisan, P.: Fed. Proc. 18:428, 1959. 6. Oaks, W.; Lisan, P., and Moyer, J. H.: Arch. Int. Med. 104:527, 1959. 7. Blohm, T. R.; Kariya, T.; Laughlin, M. W., and Palopoli, F. P.: Fed. Proc. 18:369, 1959. 8-41. Additional references available on request.

For detailed professional information, write The Wm. S. Merrell Company, Cincinnati 15, Ohio

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new
an antihistamine
that is an antihistamine
–not a somnifacient

RAPID ACTING

drowsiness *(other side effects)* rare, relief prompt, toxicity low

Investigators cite this new antihistamine's lack of side effects, its speed of action and its excellent tolerance. Nineteen investigators have treated over 800 patients with ALLERCUR. In 297 recent cases, 91% were side-effect-free. ALLERCUR is supplied in bottles of 100 scored tablets, each containing 20 mg. Clemizole HCl. Average dose is 2 to 4 tablets daily.

when allergies occur

Rx ALLERCUR®

(Clemizole HCl)

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®Trademark, Schering, A. G., Berlin Bibliography available on request.

in arthritis and allied disorders

Butazolidin®

Proved by a Decade of Experience
Confirmed by 1700 Published Reports
Attested by World-Wide Usage

Since its anti-inflammatory properties were first noted in Geigy laboratories 10 years ago, time and experience have steadily fortified the position of Butazolidin as a leading nonhormonal anti-arthritic agent. Indicated in both chronic and acute forms of arthritis, Butazolidin is noted for its striking effectiveness in relieving pain, increasing mobility and reducing inflammatory changes.



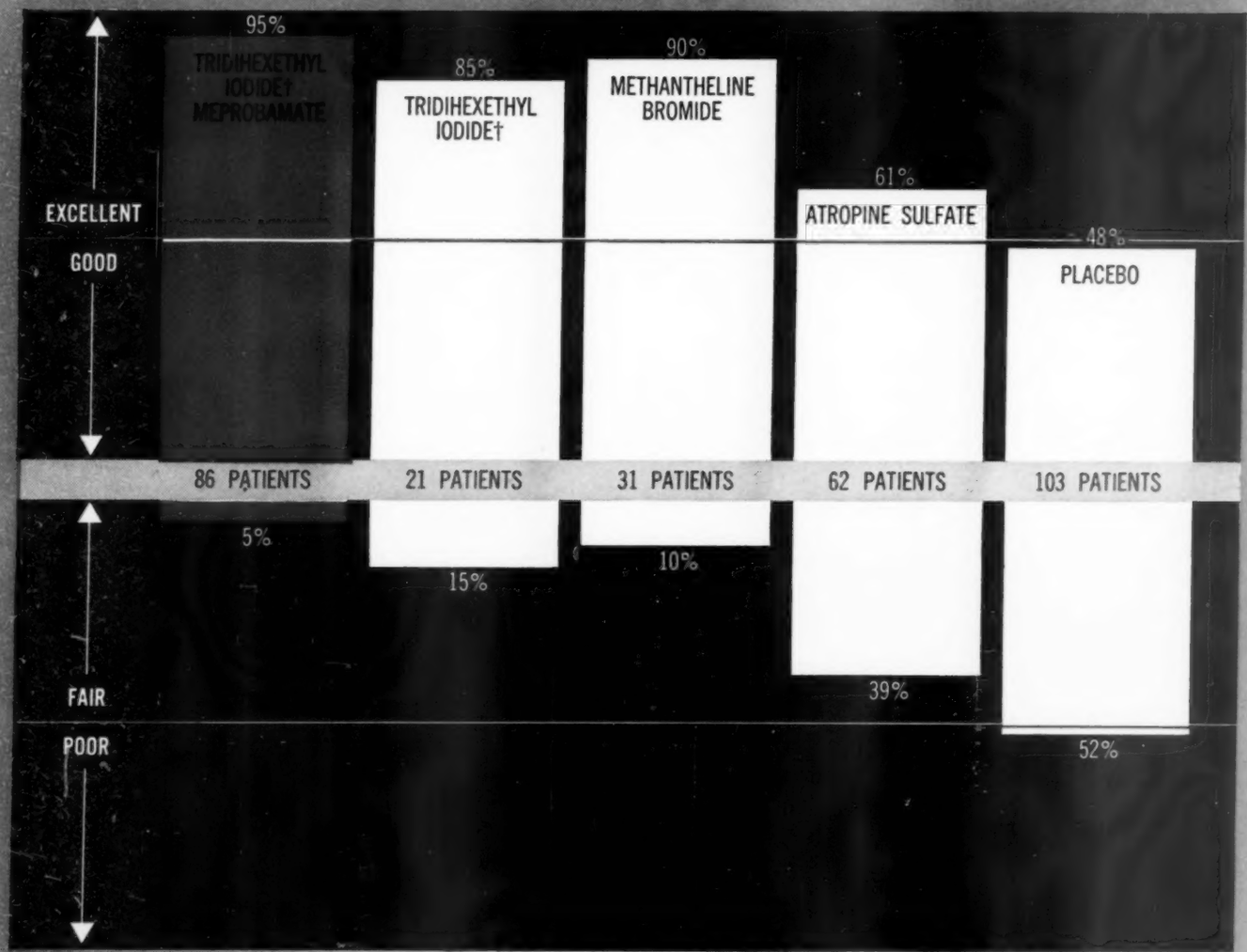
Butazolidin®, brand of phenylbutazone: Red, sugar-coated tablets of 100 mg. Butazolidin® Alka: Orange and white capsules containing Butazolidin 100 mg.; dried aluminum hydroxide gel 100 mg.; magnesium trisilicate 150 mg.; homatropine methylbromide 1.25 mg.

Geigy, Ardsley, New York

162-60

clinically proven efficacy..

in relieving tension . . . curbing hypermotility and excessive secretion in G. I. disorders



PATHIBAMATE combines two highly effective and well-tolerated therapeutic agents:

Meprobamate—widely accepted tranquilizer

and

PATHILON tridihexethyl chloride—anticholinergic noted for its effect on motility and gastrointestinal secretion with few unwanted side effects.

Contraindications: glaucoma, pyloric obstruction, and obstruction of the urinary bladder neck.

Two available dosage strengths permit adjusting therapy to the G.I. disorder and degree of associated tension.

Where a minimal meprobamate effect is preferred . . .
PATHIBAMATE-200 Tablets: 200 mg. of meprobamate; 25 mg. of PATHILON

Where a full meprobamate effect is preferred . . .
PATHIBAMATE-400 Tablets: 400 mg. of meprobamate; 25 mg. of PATHILON

Dosage: Average oral adult dose is 1 tablet t.i.d. at mealtime and 2 tablets at bedtime.

Pathibamate® 400 200

meprobamate with PATHILON® tridihexethyl chloride Lederle

..clinically proven safety

The efficacy of PATHIBAMATE has been confirmed clinically in duodenal ulcer, gastric ulcer, intestinal colic, spastic and irritable colon, ileitis, esophageal spasm, anxiety neurosis with gastrointestinal symptoms, and gastric hypermotility.

Pictured are the results obtained with the PATHILON (tridihexethyl iodide)–meprobamate combination† in a double-blind study of 303 ulcer patients, extending over a period of 36 months.* They clearly demonstrate the efficacy of PATHIBAMATE in controlling the symptoms.

SIDE EFFECTS	TRIDIHEXETHYL IODIDE† MEPROBAMATE	TRIDIHEXETHYL IODIDE†	METHANTHELINE BROMIDE	ATROPINE SULFATE	PLACEBO
DRY MOUTH	1%	5%	72%	46%	5%
STOMATITIS	1%	0%	28%	14%	0%
VISUAL DISTURBANCES	0%	0%	50%	34%	1%
URINARY RETENTION	0%	0%	18%	11%	1%
DROWSINESS	20%	0%	0%	0%	0%
COMPLICATIONS OR SURGERY					
HEMORRHAGE	0%	9%	3%	9%	10%
PERFORATION	0%	0%	0%	6%	0%
OPERATION	0%	5%	5%	14%	2%
RECURRENCES					
NONE	28%	23%	25%	17%	26%
FEWER AND MILDER	67%	62%	52%	37%	24%
SAME OR MORE	5%	15%	23%	46%	50%

*Atwater, J. S., and Carson, J. M.: Therapeutic Principles in Management of Peptic Ulcer. Am. J. Digest. Dis. 4:1055 (Dec.) 1959.

†PATHILON is now supplied as tridihexethyl chloride instead of the iodide, an advantage permitting wider use, since the latter could distort the results of certain thyroid function tests.

Lederle LEDERLE LABORATORIES, A Division of AMERICAN CYANAMID COMPANY, Pearl River, New York

control the tension — treat the trauma

Librium and the 66 tranquilizers

The era of tranquilizers that preceded Librium therapy saw a long succession of drugs—sixty-six by the latest count. And yet, today Librium is considered by many clinicians as the successor to this entire group. The reasons? The physician can manage *more patients* and control a *wider area* of anxiety-linked symptoms with Librium than with any tranquilizer or group of tranquilizers. Librium is the biggest step yet toward *"pure" anxiety relief* as distinct from central sedative or hypnotic action.

Consult literature and dosage information, available on request, before prescribing.

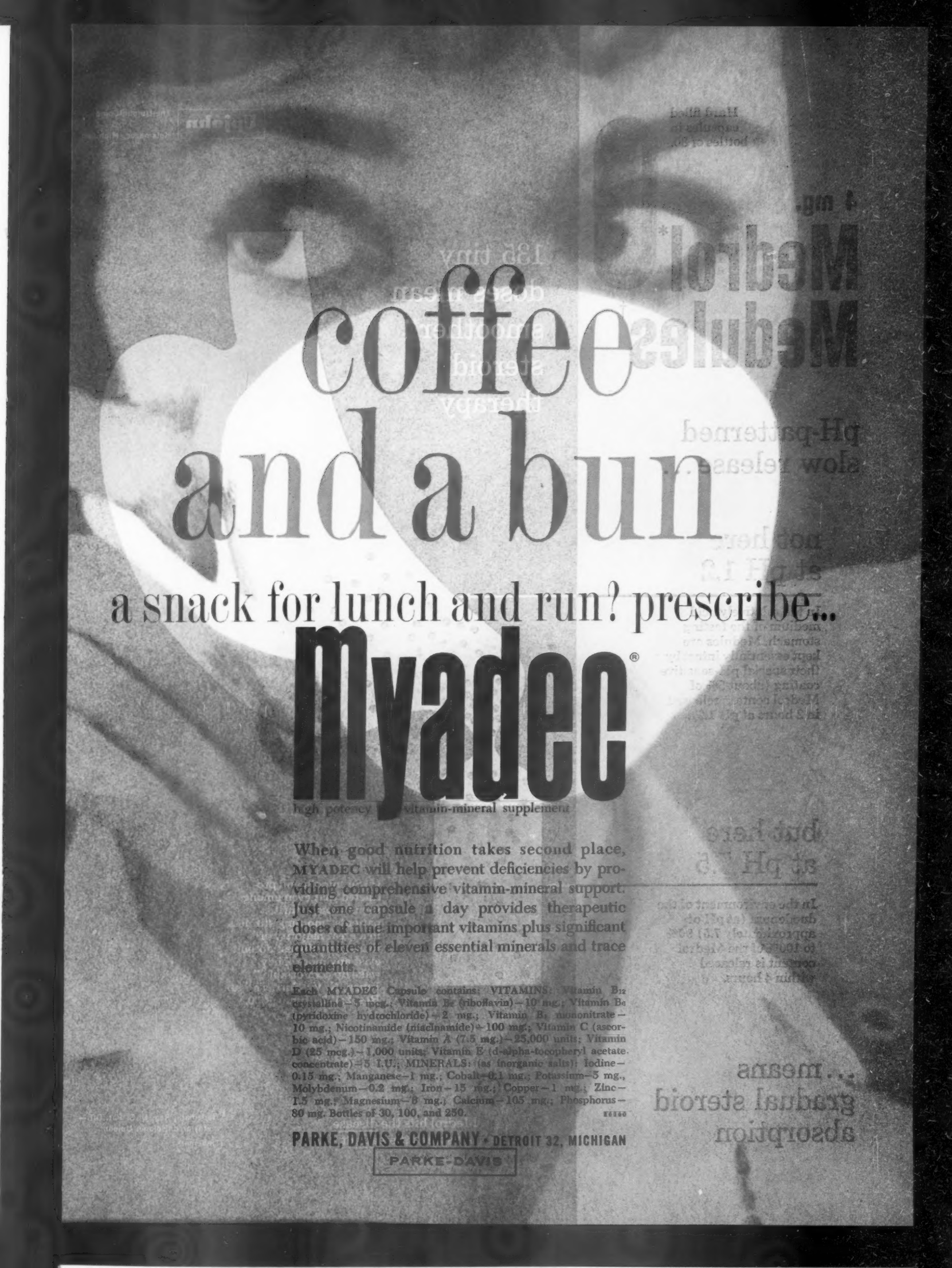
NEW LIBRIUM

the successor to the tranquilizers

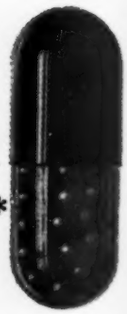
LIBRIUM® Hydrochloride—7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide hydrochloride

ROCHE LABORATORIES

Division of Hoffmann-La Roche Inc.


coffee
and a bun
a snack for lunch and run? prescribe...
Myadec®
high potency vitamin-mineral supplement
When good nutrition takes second place, MYADEC will help prevent deficiencies by providing comprehensive vitamin-mineral support. Just one capsule a day provides therapeutic doses of nine important vitamins plus significant quantities of eleven essential minerals and trace elements.
Each MYADEC Capsule contains: VITAMINS: Vitamin B12 crystalline—5 mcg.; Vitamin B2 (riboflavin)—10 mg.; Vitamin B6 (pyridoxine hydrochloride)—2 mg.; Vitamin B1 mononitrate—10 mg.; Nicotinamide (niacinamide)—100 mg.; Vitamin C (ascorbic acid)—150 mg.; Vitamin A (7.5 mg.)—25,000 units; Vitamin D (25 mcg.)—1,000 units; Vitamin E (d-alpha-tocopheryl acetate concentrate)—5 I.U.; MINERALS: (as inorganic salts): Iodine—0.15 mg.; Manganese—1 mg.; Cobalt—0.1 mg.; Potassium—5 mg., Molybdenum—0.2 mg.; Iron—15 mg.; Copper—1 mg.; Zinc—1.5 mg.; Magnesium—6 mg.; Calcium—105 mg.; Phosphorus—80 mg. Bottles of 30, 100, and 250.
PARKE, DAVIS & COMPANY • DETROIT 32, MICHIGAN
PARKE-DAVIS

Hard filled capsules in bottles of 30.



4 mg. Medrol* Medules†

pH-patterned slow release...

not here at pH 1.2

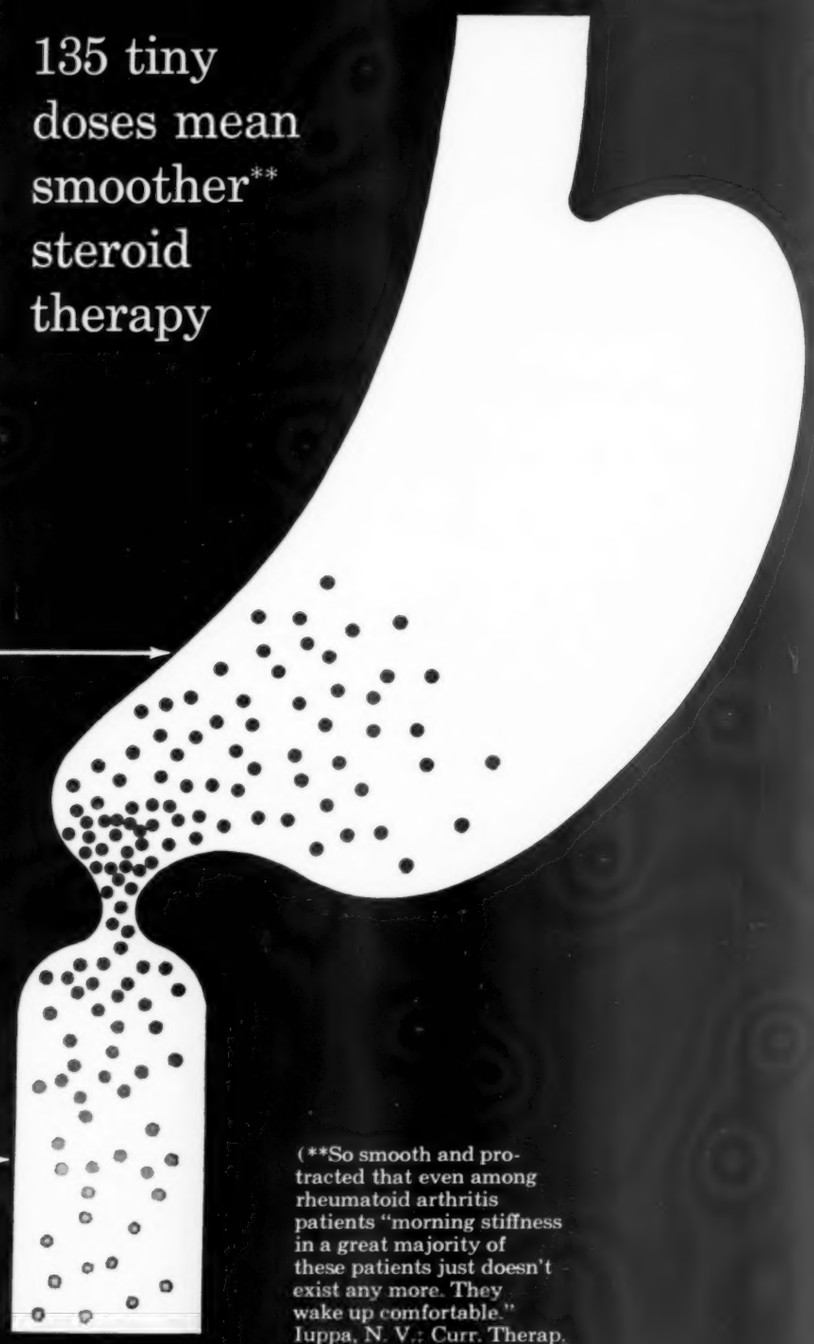
In the relatively acid medium of the fasting stomach, Medules are kept essentially intact by their special pH-sensitive coating (about 5% of Medrol content released in 2 hours at pH 1.2).

but here at pH 7.5

In the environment of the duodenum (at pH of approximately 7.5) 90% to 100% of the Medrol content is released within 4 hours.

...means gradual steroid absorption

135 tiny doses mean smoother** steroid therapy



(**So smooth and protracted that even among rheumatoid arthritis patients "morning stiffness in a great majority of these patients just doesn't exist any more. They wake up comfortable." Iuppa, N. V.: Curr. Therap. Res. 2:177 (June) 1960.)



Medrol hits the disease, but spares the patient

*Trademark, Reg. U. S. Pat. Off.—methylprednisolone, Upjohn

†Trademark

Upjohn

The Upjohn Company

Kalamazoo, Michigan

YUM

(translation: a little real salt can mean a lot in edema and hypertension)



Think of mashed potatoes without the pinch of salt. Unthinkable? Not for the edema or heart patient, who may live with such dreary fare day after day. A good diuretic like Oretic offers a chance of welcome relief from this tasteless pattern. Potent enough to treat the more serious aspects of edema, and valuable in management of mild to moderate hypertension, Oretic produces a marked elimination of water and sodium. And the saluretic effect paves the way for your exploration of revised meal plans and somewhat relaxed dietary restrictions. Oretic offers no 100% relief for low-sodium diets, of course. But adjustment should be possible in enough cases to make it worth considering on an individual basis. The individual lucky enough to get a little of the real pleasure of real salt back on the table will surely thank you.

ORETIC®
(Hydrochlorothiazide, Abbott)

a potent means when the end is saluresis. Tablets, 25- and 50-mg.

ABBOTT

007252

How to win little friends and influence recovery



Cosa-Terrabon*

oxytetracycline with glucosamine

IN BRIEF

COSA-TERRABON provides the proven safety, toleration, and broad-spectrum activity of Terramycin in preconstituted Pediatric Drops and Oral Suspension. The tasty, fruit flavor of COSA-TERRABON has great appeal to children. Decisive in action and delicious in taste, COSA-TERRABON provides the margin of difference necessary for the successful treatment of many common pediatric infections.

INDICATIONS: COSA-TERRABON is recommended for the many childhood infections caused by a wide variety of susceptible bacteria, spirochetes, and certain large viruses and parasites. Indications include infections of the respiratory, gastrointestinal, and urogenital tracts, and of other body systems and organs.

ADMINISTRATION AND DOSAGE: For infants and children, 10 to 20 mg. of Terramycin per pound of body weight daily, in divided doses, is usually effective. Therapy should be continued for 24 to 48 hours after symptoms have subsided.

wt. lbs.	daily dosage (at least 10 mg./lb.)	practical daily dosage	
		Oral Susp. 125 mg./tsp.	Ped. Drops 5 mg./drop
10	100 mg.	—	5 gtt. q.i.d.
20	200 mg.	½ tsp. q.i.d.	10 gtt. q.i.d.
30	300 mg.	½ tsp. t.i.d. and 1 tsp. h.s.	15 gtt. q.i.d.
40-50	400-500 mg.	1 tsp. q.i.d.	—
60	600 mg.	1 tsp. t.i.d. and 2 tsp. h.s.	—

PRECAUTIONS: Although adverse reactions to Terramycin are rare, if glossitis, allergic reaction, individual idiosyncrasy or other untoward effect should occur, discontinue medication. Broad-spectrum antibiotics may occasionally cause an overgrowth of nonsusceptible organisms such an monilia and staphylococci. Should such superinfection occur, replace medication with therapy indicated by susceptibility testing.

SUPPLY: COSA-TERRABON Oral Suspension — preconstituted, fruit-flavored, 125 mg. per 5 cc. (tsp.); bottles of 2 oz. and 1 pint. COSA-TERRABON Pediatric Drops—preconstituted, fruit-flavored, 5 mg. per drop (100 mg. per cc.); 10 cc. bottle with calibrated plastic dropper.

Terramycin is also available in a variety of oral, parenteral and topical forms which permit convenient administration by more than one route at a time.

Detailed professional information is available on request from Pfizer Laboratories Medical Department.

Science for the world's well-being™

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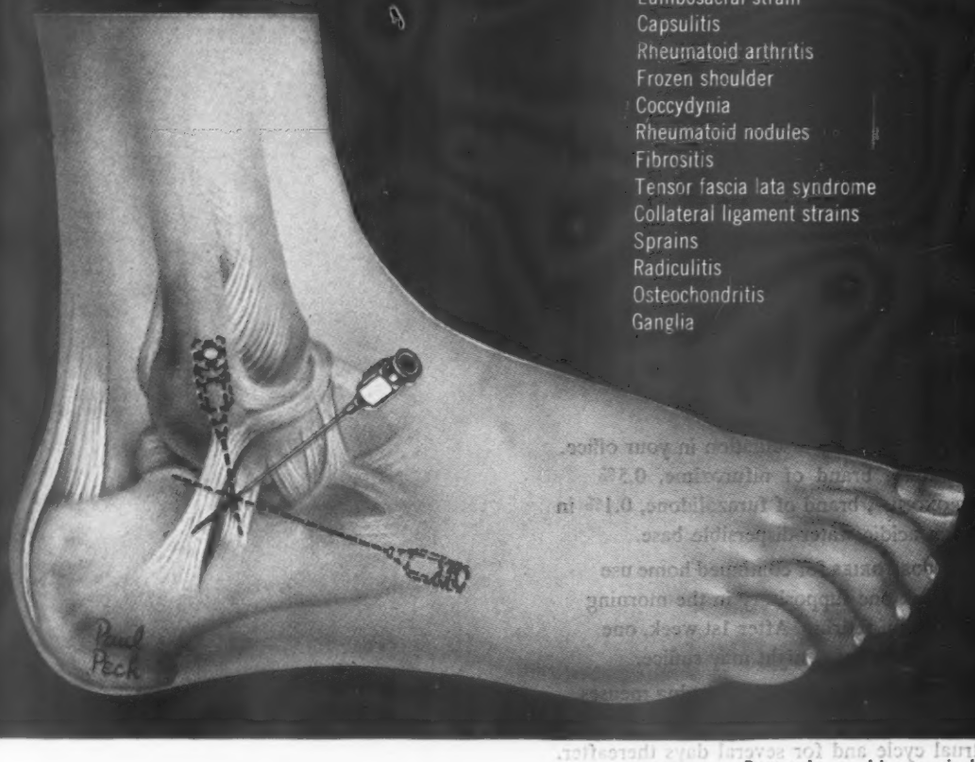
HYDELTRA®-T.B.A.

(Prednisolone *tertiary*-butylacetate, Merck)

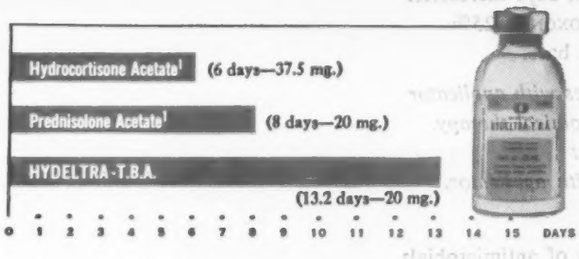
for relief that lasts—longer

in *SPRAINS*—
reduces tenderness,
swelling and
limitation of motion

- Osteoarthritis
- Acute gouty arthritis
- Bursitis
- Tendinitis
- Trigger finger
- Peritendinitis
- Trigger points
- Tennis elbow
- Lumbosacral strain
- Capsulitis
- Rheumatoid arthritis
- Frozen shoulder
- Coccydynia
- Rheumatoid nodules
- Fibrositis
- Tensor fascia lata syndrome
- Collateral ligament strains
- Sprains
- Radiculitis
- Osteochondritis
- Ganglia



Anti-inflammatory effect lasts longer than that provided by any other steroid ester



Dosage: the usual intra-articular, intra-bursal or soft tissue dose ranges from 20 to 30 mg. depending on location and extent of pathology.

Supplied: Suspension 'HYDELTRA'-T.B.A.—20 mg./cc. of prednisolone *tertiary*-butylacetate, in 5-cc. vials.

MERCK SHARP & DOHME
DIVISION OF MERCK & CO., INC.
PHILADELPHIA 1, PA.

CONSISTENTLY GOOD CLINICAL RESULTS IN TRICHOMONAL AND MONILIAL VAGINITIS

TRICOFURON IMPROVED (Suppositories and Powder) cured 143 of 161 patients with vaginitis due to Trichomonas vaginalis, Candida (Monilia) albicans, or both. "Almost immediate symptomatic improvement was noted with the first insufflation."

Criteria for cure: freedom from infecting organisms as well as symptoms on repeated examinations during a three-month follow-up This cure rate of 88.8% is "surprisingly similar" to results reported by earlier investigators.

Coolidge, C. W.; Glisson, C. S., and Smith, A. S.: J.M.A. Georgia 48:167, 1959.

TRICOFURON®

IMPROVED

2-step treatment brings swift relief, eradicates stubborn trichomonads, Candida (Monilia) albicans, Hemophilus vaginalis

1. **POWDER** for weekly insufflation in your office. MICOFUR®, brand of nifuroxime, 0.5% and FUROXONE®, brand of furazolidone, 0.1% in an acidic water-dispersible base.

2. **SUPPOSITORIES** for continued home use —1st week one suppository in the morning and one on retiring. After 1st week, one suppository at night may suffice.

Continue use of suppositories during menses. Treatment should be continued throughout a complete menstrual cycle and for several days thereafter. MICOFUR 0.375% and FUROXONE 0.25% in a water-miscible base.

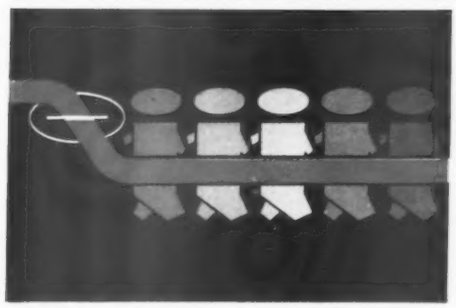
Rx new box of 24 suppositories with applicator for more practical and economical therapy.
Also available:
box of 12 suppositories with applicator.

NITROFURANS—a *unique* class of antimicrobials
EATON LABORATORIES, NORWICH, NEW YORK

making oral blood-sugar control a reality for more diabetics

Diabinese®

brand of chlorpropamide



IN BRIEF

DIABINESE, a potent sulfonylurea, provides smooth, long-lasting control of blood sugar permitting economy and simplicity of low, once-a-day dosage. Moreover, DIABINESE often works where other agents have failed to give satisfactory control.

INDICATIONS: Uncomplicated diabetes mellitus of stable, mild or moderately severe nonketotic, maturity-onset type. Certain "brittle" patients may be helped to smoother control with reduced insulin requirements.

ADMINISTRATION AND DOSAGE: Familiarity with criteria for patient selection, continued close medical supervision, and observance by the patient of good dietary and hygienic habits are essential.

Average maintenance dosage is 100-500 mg. daily. For most patients the recommended starting dose is 250 mg. given once daily. Geriatric patients should be started on 100-125 mg. daily. A priming dose is not necessary and should not be used; most patients should be maintained on 500 mg. or less daily. Maintenance dosage above 750 mg. should be avoided. Before initiating therapy, consult complete dosage information.

SIDE EFFECTS: In the main, side effects, e.g., hypoglycemia, gastrointestinal intolerance, and neurologic reactions, are related to dosage. They are not encountered frequently on presently recommended low dosage. There have been, however, occasional cases of jaundice and skin eruptions primarily due to drug sensitivity; other side effects which may be idiosyncratic are occasional diarrhea (sometimes sanguineous) and hematologic reactions. Since sensitivity reactions usually occur within the first six weeks of therapy, a time when the patient is under very close supervision, they may be readily detected.

PRECAUTIONS AND CONTRAINDICATIONS: If hypoglycemia is encountered, the patient must be observed and treated continuously as necessary, usually 3-5 days, since DIABINESE is not significantly metabolized and is excreted slowly. DIABINESE as the sole agent is not indicated in juvenile diabetes mellitus and unstable or severely "brittle" diabetes mellitus of the adult type. Contraindicated in patients with hepatic dysfunction and in diabetes complicated by ketosis, acidosis, diabetic coma, fever, severe trauma, gangrene, Raynaud's disease, or severe impairment of renal or thyroid function. DIABINESE may prolong the activity of barbiturates. An effect like that of disulfiram has been noted when patients on DIABINESE drink alcoholic beverages.

SUPPLIED: As 100 mg. and 250 mg. scored chlorpropamide tablets.

More detailed professional information available on request.

Science for the world's well-being™

Pfizer

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Division, Chas. Pfizer & Co., Inc.
Brooklyn 6, New York

anemia...
"silent
partner"
of so
many
clinical
conditions...



menorrhagia



pregnancy



geriatrics



surgery



adolescence





chronic illness

TRINSICON®
provides complete therapy for all treatable anemias

Trinsicon® (hematinic concentrate with intrinsic factor, Lilly)

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The American Journal of Medicine

VOL. XXIX AUGUST 1960 No 2

Editorial

Ionizing Radiation*

". . . a divine and terrible radiance . . ." *Alexander Dumas the Elder*

THERE is present concern regarding the hazards of increasing medical, industrial and military uses of ionizing radiation. There is no question that large doses of ionizing radiation are harmful to man. The concern is with the day-to-day exposure of the population to small amounts of radiation from these various sources. Considerable acrimonious controversy has arisen over the possible harmful results of increased exposure to radiation to this and future generations. Extreme positions have been taken by some scientists. There are those who seem to ignore any possible danger while others would, if they could, "abolish" all radiation. Neither position is practical.

Radiation is not new nor was it invented by man. The fact that radiation poses a public health problem does not make it unique and it need not result in the almost hysterical statements one reads today. The tenet that our knowledge of radiation hazards is incomplete has been held as one reason for discontinuing certain uses of radiation which might result in greater exposure of the population. It is worth pointing out that our knowledge of the effects of smog is incomplete also, yet no one has seriously suggested limiting the use of automobiles. Actually, in the area of radiation hazards methods of control have been and are being worked out. The phenomenally good radiation health record of the Atomic Energy Commission is a case in point [*1*]. Their stringent regulations imposed on the use and disposal of isotopes were instituted prior to the beginning of the present debate. Recommendations for control of medical radiation sources were made in this country in 1929 and in Britain before that time. The awareness of hazards from radiation is not new.

Much of the furor has arisen because of the "fallout" problem. This editorial is not intended to be either a defense of or an attack on continued weapons testing by our government. The problem of fallout from weapons testing is first of all a political question. While fallout has potentially grave implications with regard to health, the decision, historically at least, to manufacture and test weapons has not been based on the health-giving properties of the weapon in question. As physicians we would like to review what is known about the dangers to our patients and to ourselves from *medical* sources of ionizing radiation. If in so doing physicians have a better understanding of the hazards due to fallout, this is an unintended byproduct of our main thesis.

The physical mechanisms of the biological effects of all penetrating radiation is much the same [*2*]; the displacement of electrons from atoms and molecules, leaving a trail of positively charged atoms, molecular fragments (free radicals) and displaced electrons behind. The first phase, a purely physical process, results in secondary interactions of the primary products among themselves and with the surrounding

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medium which are chemical in nature. These chemical interactions may exert their effect either locally or at more distant sites. The possible kinds and amounts of reaction are large and the result depends not only on the tissue or tissues radiated but also upon such factors as age, sex, biologic state of the organism as well as the species radiated. These complexities are certainly partially responsible for the differing current opinions held regarding hazards from radiation.

The physicochemical interactions at a cellular level result generally in three different kinds of effects when viewed temporally. If the dose is high enough (greater than 100 rad in man) [*3*] the acute radiation syndrome may result, an illness of graded severity ranging from practically no disability to death of the organism in a relatively short time. There are various species differences in terms of sensitivity to range of absorbed dose, but none are immune to this effect. The chronic, delayed, late or "somatic" effects may appear months to years after exposure. They may vary in their manifestation by species but are also, as far as is known, an invariable result. The most prominent of these are carcinogenesis and premature death from less specific causes, the so-called "aging" effect of radiation. Of perhaps the greatest importance is the effect of radiation on the genetic apparatus, induction of mutations which may result in death or disability of the progeny of radiated persons. These latter two effects, unlike the acute radiation syndrome, may possibly occur at doses much lower than 100 rad.

To understand the present controversy, it is necessary to consider what "threshold effect" is and, most importantly, at what level of dose in the general biologic response to radiation it might occur. For these purposes, we are really only interested in low doses of radiation, that is, from 50 rad down to natural background activity. Since all known long term or delayed biologic effects of radiation are similar to recognized diseases in man, and at this stage of our knowledge inseparable, exposure to radiation of the population above background rates will simply add new cases of certain diseases in relation to the dose of radiation the population absorbs. A graphic representation of the incidence of disease versus radiation dose must of necessity start from the natural background incidence of the disease. If the population receives 20 or 50 rad prior to an increase of incidence above the background incidence, then an absolute threshold exists. If, beginning with the first increment of radiation dose above background, the amount of disease increases proportionate to dose, the relation would be linear and no threshold exists. In the same situation if the common sigmoid biologic response curve were observed, a threshold would not exist, but as a practical matter, the risk from small doses might be so low as to be negligible. This is a relative threshold. If the imagination wanders, one can conjure up both linear and sigmoid situations with and without true threshold. It is pertinent that present numerical estimates of the magnitude of the effect of low doses of radiation on human populations are predicated on the assumption that a linear situation with no threshold obtains.

In the field of genetics it is generally conceded that a "no threshold" situation best describes the relation between dose and induced genetic abnormalities [*4*]. Some reservations are nevertheless in order. The largest mammal studied in a controlled situation has been the mouse. One cannot really derive too much comfort from this, as the genetic apparatus of the mouse has been shown to be several orders of magnitude more sensitive than that of *Drosophila*. The geneticists have demonstrated linearity in *Drosophila* down to 25 rad. Studies on mice have usually been carried out with much larger doses, but histologic examination of mouse testes can demonstrate damage down to about 5 rad. More recently Russell, Russell and Kelly [*5*] have cast some doubt on the "fact" of strict linearity of radiation effects in the genetic apparatus. While linearity seems to hold for acute doses, there is evidence that the effect decreases when the dose is divided over time.

Two human studies in genetics bear on this problem: that on the Japanese survivors of the atomic bombings of Hiroshima and Nagasaki [*6*] and more recently a study on congenital malformations in New York State [*7*]. The Japanese study in which the absorbed dose was relatively large could demonstrate no evidence of an increased rate of malformations in the offspring of radiated persons. In a subsequent report [*8*] the authors pointed out that reversals in sex ratio of the newborn of exposed parents were probably due to the induction of lethal mutations in the germ plasm of the survivors. Since the sample was relatively small, the sample size might be blamed for the failure to find a definite radiation effect rather than actual absence of an effect in man. The New York State study (in which the dose was small) correlates congenital malforma-

tions in several million births positively with variation in background radiation which results from differing rock formations and differing degrees of exposure of the rock formations in upstate New York. The difficulties of ruling out effects of other factors, such as diet, consanguinity and virus infections, in a retrospective study of birth certificates of babies with congenital malformations are such that a positive correlation with radiation such as found in this study is provocative but not convincing [*9*]. This latter study, while potentially of great importance, should be viewed with caution until supporting evidence is gained.

In summary, there is general agreement that there is no threshold for genetic effects. It seems likely, however, that chronic or intermittent radiation is less effective than the same total dose delivered at a single exposure. The dose-effect relationship has not been quantitated accurately in human subjects at any level of radiation dosage. Interpolations from animal experiments have been used to estimate risk in man.

Two delayed or somatic effects have been investigated in great detail, both in experimental animals and in man. A variety of tumors have been studied, but an increased incidence of leukemia is the most uniform and striking neoplastic result of exposure to radiation in man and in some species of animals. Premature death or "life shortening," or less specifically and possibly less accurately, "aging" of an exposed population of experimental animals and perhaps human subjects is the other outstanding finding. It is in these areas that the threshold controversy rages.

Leukemia has been reported to follow human exposure to both internally deposited nuclides and external radiation [*10*]. A number of studies, however, lend themselves to a reasonable estimation of dose received by a population, have a reasonable estimate of the number of people placed at risk, and also contain fairly adequate control populations. These are the studies of Simpson and Hempelmann [*11*] on children treated with x-ray for enlargement of the thymus gland, the studies of Court-Brown and Doll [*12*] on patients receiving x-ray therapy for rheumatoid spondylitis, and the studies conducted in Japan [*13*] on survivors of the atomic bombings in Hiroshima and Nagasaki. All have demonstrated without doubt that the risk of leukemia in a human population is increased by exposure to radiation. In the British and Japanese studies estimates of the shape of the dose-response curve have been made. The British study has been interpreted as indicative of a no threshold situation for radiation directed primarily at the spinal marrow. However, the smallest dose was about 250 rad. The Japanese studies show linearity of the response above 50 rad. Below that point the data are such that no estimates are admissible. Both studies deal adequately with the shape of the response curve only at doses greater than a lower limit of 50 rad.

There are several studies which deal with response to small doses. In 1958 Stewart, Webb and Hewitt [*14*] reported the results of a survey of childhood malignancies in England. This study examined several possible etiological factors. One of the most often quoted results is the positive correlation between antenatal x-ray (maternal pelvimetry or abdominal x-rays) and childhood leukemia. According to Stewart's figures, a child who is exposed to a dose of radiation considerably less than 5 rad in utero is two times more likely to die of leukemia than a cohort. Ford, Paterson and Treuting [*15*] in this country have obtained similar results in a comparable study. The primary differences between their survey and the English survey was in selection of control subjects. On the other hand, surveys by Kaplan [*16*], Polhemus and Koch [*17*], Murray, Heckel and Hempelmann [*18*] failed to demonstrate such a positive correlation. The former studies [*14,15*] are the only direct evidence in man that small doses of radiation are leukemogenic or, more broadly, carcinogenic. In the Japanese studies the younger age groups were shown to be somewhat more sensitive to the leukemogenic effect of radiation. The studies of Stewart, Webb and Hewitt [*14*] and Ford, Paterson and Treuting [*15*] would indicate exquisite sensitivity of fetal tissue. As in the survey of subjects with congenital malformation [*7*], these findings are most provocative. There are, however, differences in the selection of control subjects and instances of malignancies not only in terms of composition but also in discrepancies in the reporting of x-ray examinations by the various disease and control groups. This is true in all studies cited. To be certain of the relation one would need to do a prospective study in which sources of memory bias can be removed and the control groups can be matched by maternal condition as well as date of birth, sex and locality of origin.

One obvious difficulty in an epidemiologic

TABLE 1
ANNUAL AVERAGE EXPOSURES TO RADIATION OF THE POPULATION AND EXPOSURES FROM COMMON MEDICAL X-RAY PROCEDURES [21]

Source of Radiation	Dose of Radiation in Millirem		
	To Gonads	To Bone Marrow	Comment
External radiation			
Cosmic rays	28	28	
Terrestial gamma rays	47	47	
			At sea level; at higher altitudes contribution from cosmic rays may be doubled
Internal radiation			
Isotopes K^{40}	19	11	
Isotopes C^{14}	1.6	1.6	
Isotopes Ra^{226}	?	38	
Fallout from weapons tests			
Sr^{90}	0.3	5.5	
Cs^{137}	1.0	1.0	
Total	97	131	
Medical procedures			
Pyelography	1,000	150	
Pelvimetry	1,500	800	
Barium enema	750	700	Average doses; highly variable with technic, age, and sex of patient
Barium meal	500	500	
Gallbladder	100	400	
Chest (14-17 film)	5	40	
Mass miniature chest x-rays	3	100	
Lumbar spine	2,000	400	

approach to the problem is the size of the population needed to demonstrate a leukemogenic effect because of the relative rarity of leukemia. A recent estimate [19] has been given that at a dose rate of 50 rad, 100,000 people would have to be studied for one full year to show a statistically significant increase in a disease that occurs with the relative infrequency of leukemia. The population size necessary for statistical significance increases exponentially as the dose decreases. These calculations are based on an assumption of linearity over all dose ranges. A non-linear relationship, in which there would probably be less effect at low doses, would be even more difficult to demonstrate by epidemiologic methods.

Using these data, however, calculations of the risk of leukemia for a population exposed to doses of radiation approaching background have been made by numerous authors and groups, notably by Lewis [20]. Lewis stated clearly that he was making an assumption of linearity of dose response at low levels, not applying experimentally derived facts. The Lewis calculations have been used to estimate the number of cases of leukemia resulting from fallout and medical uses of radiation, both of which usually fall into the area in which linearity is unproved. The United Nations report [21] also estimated from these data a risk from small doses. The report emphasized the equal possibility of no effect as regards induction of leukemia from small doses. Ignoring arguments over mechanism of induction of leukemia in man, it can be said that the dose-response relationship below 50 to 100 rad is uncertain in both man and lower animals, and that the relation could be either threshold or non-threshold.

The situation with regard to radiation-induced premature aging in man is even less firmly established than radiation leukemogenesis. The only human studies reported at present deal with longevity of American and British radiologists. These three investigations gave contradictory results. One American study [22] purported to show an earlier age of death among radiologists by approximately five years than for the general population. The British study [23] could demonstrate no such difference. Court-Brown and Doll, the authors of the British report, have criticized the methods of analysis used in the studies made in this country. They point out that in the American study the average age of death of radiologists was contrasted with the average age of death of physicians other than radiologists and with the general population. This comparison is proper only if appropriate adjustments are made for differing age compositions of the populations under study and the comparisons cover the same time periods. However, in both studies an increased rate of leukemia and cancer in general was shown in radiologists, particularly those who were in the practice of radiology prior to 1920. There is serious question that an earlier age of death has been demonstrated. More recently, Seltser and Sartwell [24] compared the age specific death rates of American radiologists and pathologists. No significant difference was found. There was again an apparent excess of leukemia among the radiologists. The fact remains that dosage is simply not known and probably is far greater than the current area of interest represented by the threshold controversy. The studies underway in Japan on atomic bomb survivors seem reasonably certain to supply an answer at least in the larger dose ranges. There seems little reason to question the likelihood of a life shortening effect in man, but its quantitative importance at small doses is open to serious question [25].

We have purposely omitted a discussion of the differences in total versus partial body radiation, chronic versus single acute exposures, internally

TABLE II
LEUKEMIA RISK FOLLOWING THERAPY OF BENIGN DISEASE

Primary Disease	Effective Radiation Dose (rad)	Estimated "New" Cases of Leukemia per 100,000 People per Year*	General Population Rate
Hyperthyroidism	10–20 total body†	1–2 per year‡	3.3 cases per year
Rheumatoid spondylitis	250–500 to spinal marrow	12.5–25 per year	3.3 cases per year

* The assumption is made that the risk following exposure to radiation is constant throughout life for the exposed subjects.

† The average total body dose or dose to the blood is about 1 rad/mc. of I^{131} [*29*].

‡ Based on estimates of risk calculated from sources cited in text and assuming populations with ages distributed from thirty-five to forty-four years.

deposited nuclides versus external radiation, and the variations in biological effectiveness of these differing situations and radiations. We all have practical awareness of the difference in 4,000 rad delivered over a long period of time in divided doses to different sites of the body and 400 rad total body radiation delivered as a single dose. The first dose is not uncommon in a protracted case of Hodgkin's disease. Beyond the therapeutic effect and some adverse effects on specific organs, the patient is not usually killed by the radiation. The latter situation, ten times less radiation, stands an excellent chance of killing the patient. It certainly will produce a serious, life-threatening illness immediately. There is really no reason at present to think that comparable differences do not exist in the many other variations in exposure to radiation. Experimentally many have been shown to exist. It is probably improper to estimate effects of small doses of strontium-90, for instance, on the basis of our knowledge of the effect of external total or partial body radiation, even if we knew with certainty that the relation of dose to occurrence of disease was directly proportional at all dose levels.

It would be nihilistic to deny the propriety of estimates of risk from small doses based on our present scanty knowledge. However, such estimates should be recognized for what they are: "Bad estimates rather than no estimates at all" [*26*]. Sir Macfarlane Burnet [*27*] has reasoned from present evidence that no more than 10 per cent of "naturally" occurring leukemia is a result of radiation. There is no statistical evidence of an increased rate of leukemia as a result of fallout. In fact, prior to the widespread use of artificially produced radiation an increase was manifest [*28*]. Lack of evidence could of course mean that our present statistics are too poor to reveal the small increases which may in truth be present. One can derive no comfort from the anonymous or unidentified status of the cases of leukemia or congenital malformations which might be due to small doses of radiation. The comfort, if any, comes from the fact that anonymity could as well be explained at the present time by lack of existence.

It is of final interest to this thesis to examine the estimated doses of radiation from various sources; background radiation, fallout and common medical procedures, and compare these with current knowledge of risk for the best quantitated effect in man at larger doses. Table I is a composite of some of the most interesting data [*27*]. All these procedures or sources of radiation contribute doses in the region of controversy. Exceptions are those of x-ray treatment of rheumatoid spondylitis and possibly I^{131} treatment of thyroid disease [*29*] listed in Table II. Here we have tentatively estimated the risk of the therapy based on the assumption of linearity of response. Whether a threshold does or does not exist, it is apparent that the magnitude of increased risk is relatively small even in the situations utilizing therapeutic doses. The question, then, is a simple one. Is the gain from any of the procedures or sources of radiation less or greater than the risk incurred? No proper medical answer can be given for the political question of fallout. A general answer for the strictly medical situations can be arrived at. In most instances it appears that the gain is considerably greater than the risk. This applies equally well to pelvimetry, I^{131} treatment and possibly x-ray treatment of rheumatoid spondylitis. To be kept in mind are the relative merits and dangers of alternatives to the use of x-ray for

diagnosis or treatment. For instance, what is the risk of surgery or long term thiouracil treatment of hyperthyroidism or the use of phenylbutazone in rheumatoid spondylitis as opposed to the risk from radiation?

The new general awareness of possible hazards from small doses of radiation only illustrates again that few things in this world are totally good. There is, however, danger of overemphasizing the harmful aspects of radiation. We have not discarded quinidine or penicillin from our therapeutic armamentarium because of the risks attendant to their use. Neither should we cast aside in haste certain well established and useful diagnostic and therapeutic measures which employ ionizing radiation.

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Clinical Studies

Cyclical Edema and Shock Due to Increased Capillary Permeability*

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We have recently had under our care an otherwise apparently normal young woman who on repeated occasions had such a sudden and marked leak of plasma from her vascular bed that she would go into profound hypovolemic shock. Because of the striking relationship of these shock episodes to the menstrual period, a hysterectomy and later a bilateral oophorectomy were performed. For a time she was thought to have been cured by the oophorectomy, but then the shock episodes recurred. Finally, during one period of shock, she died. Although we were able to study this patient intensively for nearly two years, we still are largely ignorant about the reason for the periodic sudden and striking increase in the permeability of the capillaries. Because of the unusual nature of this case, we wish to report our observations on this patient in some detail.

The patient was a thirty-four year old white woman of Italian descent who had been in excellent health until the age of thirty-two. She had had no serious illnesses in the past, specifically no known streptococcal infections. Her menarche occurred at the age of thirteen and her periods had always been regular every twenty-eight days, lasting from five to seven days without menometrorrhagia. She had never suffered any menstrual or premenstrual tension or other symptoms until the onset of her present illness. She had two uneventful full term spontaneous deliveries at ages twenty-nine and thirty-one. Both offspring are living and in excellent health. A benign breast tumor, diagnosed by tissue examination as chronic fibrocystic disease of the breast, was removed when she was thirty-two years old. She had no history of allergy or psychoneurosis. She had six siblings, who were all in good health. There was no family history of menstrual disorders or of allergies except for a maternal uncle who had bronchial asthma.

The patient was entirely well until February 1956 when, following one day of mild rhinorrhea and two days before her menstrual period was due, she awoke to note that her lower right forearm was swollen and that her voice was hoarse. Shortly thereafter nausea and vomiting developed, and she noted generalized swelling of the face, neck and all extremities. The nausea and vomiting subsided after thirty-six hours coincidentally with the appearance of her menstrual flow, but the generalized swelling persisted for about four days. She was seen by her family physician who made a diagnosis of rheumatism and treated her with aspirin and a ten-day course of penicillin injections. She was then perfectly well for five months. Her next four periods occurred regularly and were not associated with any unusual symptoms. However, in July 1956, one day after the onset of her period, she again awoke with generalized swelling, nausea and vomiting, and on this occasion also noted palpitations and shortness of breath. She was treated with penicillin and prednisone for a few days and her symptoms cleared entirely. At this time she was referred to The New York Hospital where she was examined in the general medical clinic. No abnormalities were detected on physical examination. It was thought that she was suffering from severe premenstrual salt retention [*1*]. No treatment was instituted. She was told to report promptly to the Emergency Room if another attack occurred.

She was then well for eight months, her menstrual periods occurring regularly approximately every twenty-eight days and not associated with any swelling or gastrointestinal complaints until March 1957, when one day premenstrually she noted onset of fatigue, malaise and hoarseness in the late afternoon. Within a few hours another attack of nausea, vomiting and generalized swelling developed. Her period began the next day and the vomiting subsided at the same time. The swelling gradually disappeared over the next three days.

She felt well for ten days, but then in mid-cycle (fourteenth day) had recurrence of the same symp-

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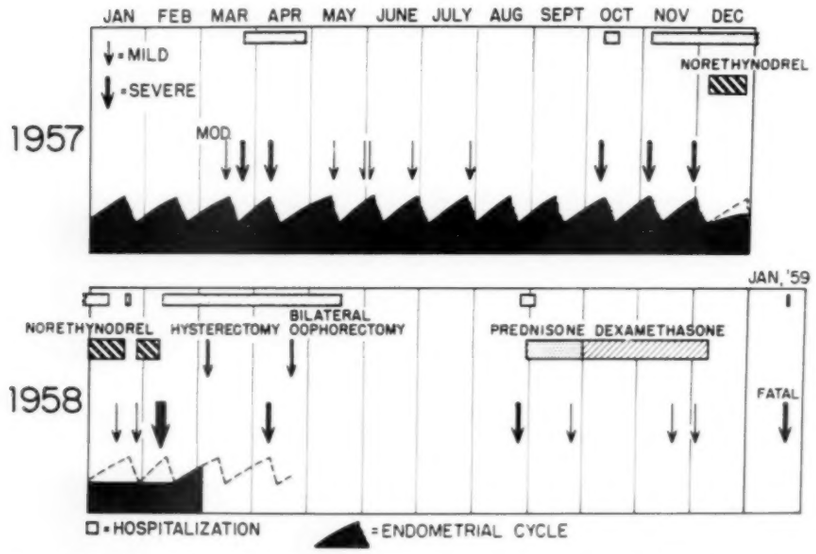


FIG. 1. Time relation of episodes of shock to menstrual cycle and to therapeutic endeavors. Two previous moderately severe episodes of shock occurred in mid-February (two days premenstrually) and in mid-July (second day of period) of 1956 which are not charted. *Mild* refers to swelling of face and extremities, weakness, weight gain of 1 to 5 kg., no significant hypotension and slight or no hemoconcentration. *Moderate* refers to marked generalized edema, weakness, vomiting, postural hypotension, variable hemoconcentration. *Severe* refers to profound shock, marked hemoconcentration, cyanosis, evidence of cardiac and renal damage. During the period of intermittent nor-ethynodrel therapy, withdrawal uterine bleeding occurred on each occasion two days after interrupting nor-ethynodrel therapy.

toms. She was admitted to The New York Hospital on March 24, 1957. The patient was followed closely since this initial admission for recurrent episodes of shock. She was studied intensively during the episodes of shock while in the hospital, and a careful record was kept of all her symptoms and their relation to her menstrual cycle while she was at home between admissions. Starting with the March 23, 1957, admission she had a total of nine severe episodes of shock and at least eleven minor episodes. (Fig. 1.) Before an artificial menopause was induced, all the severe attacks occurred from one to four days before the menstrual flow began, except for the March 23 episode, which occurred in mid-cycle. The minor attacks occurred three to six days premenstrually, or else two to three days after the menstrual flow had started.

The attacks varied considerably in severity, from a sense of tiredness with slight swelling of one wrist in the mildest episodes to a state of almost intractable shock in the most severe episodes. The outstanding features of the nine severe episodes of shock are shown in Table I. Treatment of the several severe episodes varied, but as we gained knowledge of the mechanism responsible for her state of shock (i.e., rapid loss of plasma from the vascular compartment due to a generalized increase in capillary permeability) we were able to treat her more rationally. As all the episodes were similar, varying only in severity and according to the treatment employed, we will describe just one of them in detail. This episode occurred while she was under our observation on the metabolic pavilion.

The patient had two severe episodes of shock occurring premenstrually with consecutive periods which began October 10 and November 6, 1957. (Table I.) Her next period was due on December 3 and we were not anticipating any symptoms until about November 30. She remained completely asymptomatic and afebrile, being active and most helpful towards some of her more handicapped roommates until November 28. She felt well until lunch time when she noted slight malaise. She began to feel chilly about 6:00 P.M. but ate her supper as usual. Shortly thereafter she began to feel warm and flushed, and at 7:00 P.M. her temperature was 39.3°C. Physical examination was within normal limits except for the fever, warm dry skin and a tachycardia of 124 per minute. There was no edema and the blood pressure was 112/68 mm. Hg. The hematocrit was 34 per cent, as it had been that morning. The elevation in temperature persisted during the night and the next morning, rising as high as 39.8°C. at 10:00 P.M. She complained of slight rhinorrhea, hoarseness and mild suprapubic cramps, but these symptoms were minimal and she otherwise continued to feel well. She specifically

TABLE I

CHARACTERISTICS OF NINE SEVERE EPISODES OF SHOCK, AND TREATMENT EMPLOYED

Date Episode Began	Maximum Temperature During Episode (c.)	Edema	Weight Gain (kg.)	Lowest Blood Pressure Recorded (mm. Hg)	Maximum Hematocrit Recorded (%)	Minimum Hematocrit After Recovery (%)	Highest Recorded Blood Urea Nitrogen (mg. %)	Treatment Employed		Complications
								Plasma or Plasma Expanders	Other	
3/23/57	38.6	+	3	0/0	74	38	25		100 mg. hydrocortisone intravenously, 5% dextrose/water	
4/ 8/57	38.7	++	4	0/0	62	29	21	1,000 cc. 6% dextran in saline	450 mg. hydrocortisone intravenously, 5% dextrose/water, 5% dextrose/saline	
10/ 7/57	38.5	+++	4	0/0	58.5	32	27	500 cc. 6% dextran in saline	Estrogen intravenously, aviator gravity (g) suit, 5% dextrose/water, levarterenol	
11/ 4/57	38.9	++++	6	0/0	60	30	31	1,500 cc. 6% dextran in saline; 500 cc. plasma; 100 cc. salt poor albumin	Diphenhydramine hydrochloride intravenously, 5% dextrose/water, levarterenol	Mild congestive heart failure in recovery phase
11/28/57	39.8	+	3	30/0	55.5	22	25	1,200 cc. plasma	5% dextrose/water, levarterenol	
2/ 9/58	39.0	++++	9	0/0	71	24.5	48	1,200 cc. plasma; 200 cc. salt poor albumin; thoracentesis, 1,400 cc. pleural fluid; phlebotomy, 500 cc. blood	5% dextrose/water, levarterenol, digitalization, diuretics, treatment pulmonary edema	Congestive heart failure, pulmonary edema and bilateral pleural effusions in recovery phase
4/ 9/58	38.2	+	2	0/0	57	24	37	350 cc. plasma	Diphenhydramine hydrochloride intramuscularly 250 mg., hydrocortisone intravenously or cortisone intramuscularly 5% dextrose/water, levarterenol	
8/25/58	40.1	++	6	0/0	67	25	95	3,300 cc. plasma; phlebotomy, 500 cc. blood	Diphenhydramine hydrochloride intravenously, hydrocortisone intravenously levarterenol, digitalization, 5% dextrose/water	
1/20/58	40.0	+	1	0/0	71	...	22	2,700 cc. plasma	Diphenhydramine hydrochloride intravenously, prednisolone 100 mg. intravenously	Cardiac arrest

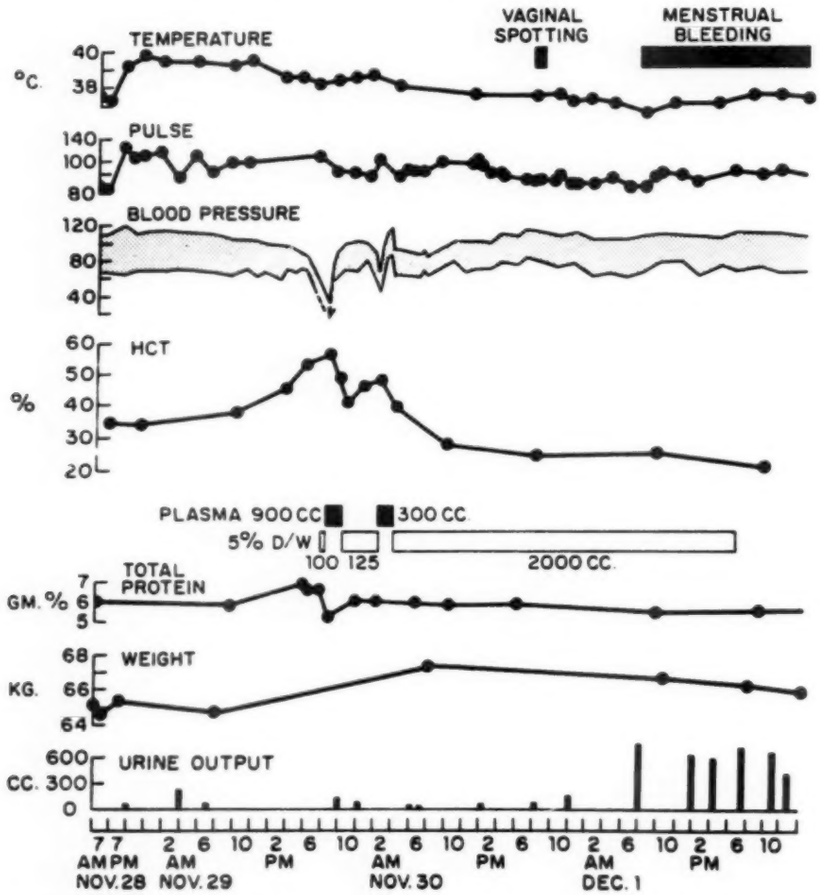


FIG. 2. Observations on the patient during an episode of shock. This episode of shock occurred while the patient was under study in the metabolic pavilion, November 1957, and is described in detail in the text.

denied the sense of tightness in her wrists, severe fatigue and nausea—the symptoms premonitory of most of her past attacks.

The blood pressure remained stable at about 110/70 mm. Hg until 8:00 A.M. the next morning when it began gradually to decline. (Fig. 2.) As the blood pressure fell, the hematocrit gradually rose. She became progressively weaker but only slight facial edema developed during the day. About 6:00 P.M. she began to have nausea and vomiting. The blood pressure continued to go down, dropping rapidly to 30/0 mm. Hg by 7:15 P.M. With the developing shock she had extreme weakness, became dyspneic and cyanotic, and complained that she was about to black out. Her hematocrit reached a high of 55.5 per cent at 7:15 P.M.

Her bed was placed on shock blocks, and plasma was infused rapidly into the intravenous needle already in place. Three hundred cubic centimeters of plasma given over fifteen minutes raised her blood pressure to 75/60 mm. Hg, and with 600 cc. additional plasma given more slowly over the next one and a half hours her pressure was raised to 100/70 mm. Hg. She continued to feel extremely weak, had frequent eructations and increased facial edema, but there was no further vomiting, dyspnea or syncope. (Fig. 3.) In sharp contrast to her usual pleasant disposition, but as in past attacks, she was very irritable and could not tolerate anything such as sheets or a blood pressure cuff touching the upper part of her body. She complained of low back pain and mild suprapubic menstrual-type cramps. At 1:00 A.M. the next morning her blood pressure again fell to 68/44 mm. Hg, and an additional 300 cc. of plasma was given. Her blood pressure then rose to 120/86 mm. Hg and thereafter remained at 88/60 mm. Hg without further therapy. Her hematocrit, which had reached a low of 41 per cent after the first 600 cc. of plasma, had gradually risen to 48 per cent during the recurrent hypotensive episode just prior to starting the last unit of plasma.

Thus a total of 1,200 cc. of plasma was necessary during this attack to keep her blood pressure above dangerously hypotensive levels. Only 225 cc. additional 5 per cent dextrose and water was given on this occasion during the period of crisis, together with an additional 2,000 cc. of 5 per cent dextrose and water

slowly over the next thirty-one hours, in contrast to large amounts of intravenous fluids given for treatment of previous attacks. Moderate facial puffiness developed, but the patient did not complain of tightness of the extremities as on past occasions, and in fact careful measurements during the crisis period showed no change in size from the asymptomatic state. It was thought that the more rigid fluid restriction prevented the marked generalized edema which had occurred in the past attacks. Even so she had considerable fluid retention, as evidenced by a weight gain of 3 kg. The maximum weight of 67.3 kg. was recorded prior to significant diuresis.

Vaginal spotting began at 6:00 P.M. on November 30, 1957, by which time the back pain, suprapubic cramps and the eructations had subsided and she was beginning to feel well. The menstrual flow was copious by the next morning. Aside from tiredness, she was asymptomatic and by that afternoon reported that she felt normal.

With the intent of suppressing her menstrual cycle, therapy with nor-ethynodrel, a 19-nor-progestational steroid containing only a slight trace of estrogen, was started on the fifth day of her cycle in dosage of 30 mg. per day. She tolerated the drug well and, except for minimal uterine cramps during the first two days of therapy, had no other symptoms. The drug was continued for twenty days and then stopped for five days to allow withdrawal bleeding which began three days after cessation of the drug and lasted three days. Therapy with nor-ethynodrel was then resumed at the same dosage for another twenty days, then stopped again to allow withdrawal bleeding. She was completely asymptomatic until the eighteenth day of the second cycle of therapy or on January 18, 1958, when she noted slight nasal congestion and hoarseness, followed two days later (twentieth day of nor-ethynodrel) by development of a typical mild attack with a rise in her hematocrit from 33 to 45 per cent. She had no fever and no hypotension on this occasion. Vaginal bleeding occurred from January 24 to 26 and therapy with nor-ethynodrel was resumed on January 26. A mild infection of the upper respiratory tract began the same day and the next day she noted malaise, marked swelling of the lower extremities, and about a 10 pound weight gain. The swelling and malaise subsided over the next three or four days and then she felt well until February 9, when another infection of the respiratory tract occurred, apparently contracted from her husband who had the "flu." Her symptoms were at first attributed to this infection but the next day vomiting and extreme weakness developed, and she eventually lost consciousness and had a short convulsion while on the toilet that evening. She was brought by ambulance to the Emergency Room and admitted.

This episode of shock and then of pulmonary edema in the recovery phase was of such severity and so intractable to methods of therapy which had previously been successful that we feared she might not survive another attack. Not only did she nearly die in shock, and later in acute pulmonary edema, but also the prolonged period of hypotension and tissue anoxia resulted in severe cardiac and renal damage manifested by disturbingly persistent electrocardiographic abnormalities and azotemia lasting for two weeks.



FIG. 3. *Top*, patient during an asymptomatic period. *Bottom*, during an episode of severe shock.

As we were impressed by the striking relationship of her shock episodes to the menstrual cycle, it was considered imperative that something be done to prevent her from having another period. It was clear that the 19-nor progestational steroid could not be relied upon to prevent her from going into shock.

At the time, an attractive hypothesis was that endometrial products were entering the circulation in the premenstrual period and were in some way responsible for the increased capillary permeability [*2–4*]. Further, it was reasoned that if an artificial menopause were induced first by oophorectomy and if a cure resulted, it would never be known whether the uterus or the gonads were the offenders. For these reasons it was decided to perform a hysterectomy first. Accordingly on March 5, 1958, a total hysterectomy was performed by Dr. James McNeil. Careful abdominal exploration was carried out at the time of the operation and no abnormalities were discovered. In particular the liver, spleen, retroperitoneal nodes, adrenals and kidneys were palpated with great care and no enlargement or masses were detected. The normal-appearing ovaries were placed in the cul-de-sac so they would be accessible for a vaginal oophorectomy, if this later proved necessary. The resected uterus had a small subserous myoma, but was otherwise unremarkable grossly. Microscopic examination showed a normal proliferative endometrium with a minimal degree of adenomyosis. A slight chronic cystic cervicitis was also present. No other abnormalities were noted.

The patient's postoperative course was entirely uneventful. Her hematocrit and vital signs remained stable. On the basis of daily vaginal smears, which were resumed a few days postoperatively, it was estimated that her next period would have commenced March 18 and that ovulation would therefore occur on March 31. A distinct 0.3°C. rise in basal body temperature occurred on April 1 and persisted to verify the day of ovulation. She remained asymptomatic until the evening of April 9, 1958, or five days before her next period would have been expected to begin. She then proceeded on schedule to have another typical shock episode. She was treated with rather large doses of intravenously and intramuscularly administered cortisone and intramuscularly administered diphenhydramine hydrochloride on this occasion in an attempt to alter the presumed allergic response thought to be responsible for her state of shock. It is impossible to say whether this therapy was of benefit, but in any case this attack was less severe than the previous one.

As this episode of shock was in all respects entirely similar to those suffered prior to hysterectomy, including premenstrual timing, it was agreed by all that oophorectomy was now indicated as soon as she was judged to have recovered satisfactorily. On April 21, 1958, a vaginal oophorectomy was performed by Dr. James McNeil. The ovaries appeared normal grossly, and microscopically showed only a slight to moderate degree of peripheral sclerosis, no other abnormalities being found. The postoperative course was complicated by the development of a rising temperature which went as high as 39.4°C. on the fifth postoperative day. This was thought to be due to a pelvic cellulitis and the fever subsided gradually while she was receiving penicillin and streptomycin therapy. She became afebrile and asymptomatic after the eighth postoperative day. A febrile reaction to the oophorectomy *per se* could not be definitely excluded, however. The patient's hematocrit, which had been 33 per cent immediately after surgery, fell to a low of 24 per cent on the seventh postoperative day. This was attributed to blood loss suffered during the operation, and an eight-day course of Imferon, 2 cc. administered intramuscularly each day, was given. Her hematocrit rose gradually to a level of 40 per cent by June 13, 1958.

The patient remained well for four months following oophorectomy. She regained her strength and was able to perform all her regular housework, and to care for her two children. Menopausal symptoms were minimal and consisted only of occasional mild warm flushes, usually at night. She had no episodes of edema and her weight remained stable around 135 pounds without fluctuation of more than 2 pounds. Late in June a new symptom developed—an unexplained pain in the right shoulder, which radiated down the lateral aspect of her arm to the tips of her fingers and was sometimes accompanied by tingling of the finger tips. There were no other arthralgias or parasthesias. No objective signs of inflammation or neurological abnormalities were found. The pain was not incapacitating and was almost entirely relieved by the injestion of aspirin. These symptoms persisted intermittently for about a month and then subsided spontaneously. The only other symptoms or signs which the patient and her physicians were able to detect during this four-month period were the occasional sensation of bloating of the abdomen and a rather persistent and localized 2 cm. area of puffiness beneath the left lower eyelid. Her blood pressure was consistently normal around 130/80 mm. Hg.

During this four-month period following oophorectomy, these trivial symptoms and her general excellent state of health led us to think she had been cured by the operation. Daily vaginal smears showed a postmenopausal pattern with a low level of estrogenic activity, as is commonly seen following oophorectomy. The only disturbing findings were an eosinophilia of 5 per cent and persistent abnormalities in the patient's serum globulins two months postoperatively. The serum protein abnormalities will be described in detail later, along with the other laboratory studies.

About mid-August a dry cough developed for which she was given a cough syrup by her local family physician. This subsided but recurred about two weeks later, when she also noted recurrence of pain in the right shoulder and numbness in the fingers of the right hand. Two days after the cough recurred, she awoke on August 25 with severe malaise, weakness and vomiting. She came to the Emergency Room where it was immediately apparent that she was again in shock. This attack was entirely similar to the ones

suffered preoperatively. Obviously the thesis that she might be manifesting an autoimmune reaction to some ovarian product was no longer tenable. On the other hand it still seemed most plausible to us that the shock episodes represented some type of hypersensitivity reaction. An exhaustive re-exploration was made of the patient's dietary and other habits. We were unable to identify any suspicious antigens, such as a particular food or medication, which had been consistently ingested prior to her shock episodes. Actually her medications while at home had consisted solely of aspirin or acetophenacetin and cough medicine, and she had taken each on several occasions without any ill effect whatever. Some shock episodes had taken place without her having taken any medication at all. Despite this failure to incriminate any specific allergen, either endogenous or exogenous, it was decided that prophylactic antihistaminic and adrenal steroid therapy should be the next step in attempting to prevent the shock episodes.

Following discharge from the hospital she continued on prednisone and diphenhydramine hydrochloride 50 mg. administered three times a day. Except for occasional mild flushes, she remained well for about four weeks until September 23, when rather suddenly tightness and swelling of all her extremities developed and she noted a weight gain of 3 kg. There were no symptoms suggestive of an infection of the respiratory tract on this occasion. She was admitted overnight to the Emergency Room but this proved to be an abortive attack, as her blood pressure did not fall and she did not have vomiting, fever or hemoconcentration.

Dexamethasone was substituted for prednisone following this mild attack, first in dosage of 0.5 mg. administered four times a day and then 0.5 mg. three times a day in the hope that there would be less progression of Cushingoid features on this steroid. However, more prominent Cushingoid facies continued to develop progressively together with a marked growth of lanuginous facial hair, erythema of the upper trunk and a striking increase in appetite. She became quite obese, the weight gain being predominantly in the face, upper arms and abdomen. Despite therapy with Dexamethasone, two further episodes of edema and a sudden weight gain of 4 kg. occurred on November 19 and December 2. As Dexamethasone therapy seemed ineffective in preventing periodic edema and fluctuations in weight, and as the induced Cushingoid obesity was becoming marked and was causing her considerable discomfort and embarrassment, it was decided to taper off and stop administration of the drug at this point. She received no further doses of dexamethasone after December 8. She then remained well with no further fluctuation in weight of more than 1 kg. until January 20, when her final episode of shock began.

Because it had been noted that many of her episodes of fluid retention and shock followed shortly after an infection of the respiratory tract, she had been warned to avoid contact with anyone who had such an infection. However, her daughter had a cold around mid-January. On January 19 the patient herself noted the onset of nasal stuffiness and mild sore throat. She took 25 mg. of diphenhydramine hydrochloride and 2 tablets of acetophenacetin and went to bed. The next morning when she awoke she felt faint and weak, noted that her face and extremities were swollen, and began vomiting. She was brought to the Emergency Room, having to be carried in on a stretcher because of weakness and postural syncope. As usual during a severe attack, she was agitated and apprehensive but quite rational and alert.

Treatment, as in the past, consisted of plasma infusion and parenterally administered diphenhydramine HCl and adrenocorticosteroids (on this occasion intravenously administered prednisolone, 100 mg. by continuous drip). It was possible to keep her systolic blood pressure around 70 mm. Hg with constant slow infusion of plasma and she apparently was doing satisfactorily. In fact, in contrast to the severe ischemic changes seen with prior episodes of shock, an electrocardiogram taken shortly after admission was almost normal, except for a sinus tachycardia of 136 per minute, and showed considerable improvement over the most recent previous electrocardiogram taken during the recovery phase of the last serious shock episode in August 1958.

By 4:45 the next morning she had received 2,700 cc. of plasma over the seventeen hours since admission. At this time her pulse was regular at 90 per minute, her systolic blood pressure remained stable at about 70 mm. Hg, she was oriented although agitated, and there was no evidence of congestive failure. Suddenly, and without any warning, she gasped, her eyes rolled up, and no heart sounds or pulse could be detected. She had several more gasping inspirations and then respiratory movements ceased. The chest was opened immediately and it was found that her heart was in asystole. Despite cardiac massage, intracardiac administration of levarterenol and the usual resuscitation procedures, cardiac action could not be restored. She was pronounced dead approximately twenty hours after the start of this attack.

STUDIES

Blood. Hemograms prior to the patient's present illness were entirely normal, without eosinophilia. The last complete blood count before her first admission for shock (but following the first two episodes of shock suffered at home) on August 28, 1956, was entirely normal except for a 7 per cent eosinophilia. After the episodes of cyclical shock began the red blood cell and white cell values fluctuated widely.

Erythrocytes: During periods of shock the hema-

tocrit rose on different occasions up to 56 to 74 per cent. As the hematocrit fluctuated somewhat even during the asymptomatic periods, it was difficult to be sure what the base line hematocrit was at any given time. However, this seemed to be about 38 per cent after the first admission for shock in April 1957 and gradually fell to about 32 per cent by January 1958. A determination of the red cell mass, employing the patient's own cells tagged with Cr^{51}, was made on April 7, 1958, at a time when her hematocrit was 40 per cent (three days prior to an episode of shock). This showed a red blood cell volume of 1,128 cc. or 18.9 cc. of red blood cell volume per kg. (normal is 25 to 35 cc. per kg.). The patient was completely asymptomatic at the time this study was made. The hematocrit the day preceding the test was 39 per cent and the day following the test was 34 per cent; two days later, on April 10, 1958, during an episode of shock, it rose to 57 per cent. The Cr^{51} survival study could not be completed because it was invalidated by the marked alterations in hematocrit. However, there was never any evidence of hemolysis.

Following the two surgical procedures, the hematocrit leveled off at about 30 per cent in April 1958. Although smears and red blood cell indices failed to show evidence of microcytosis or hypochromia, she was given a course of parenteral iron therapy to overcome the operative blood loses. Thereafter her hematocrit rose gradually within six weeks to 40 per cent and this was taken as her base line hematocrit for the remainder of her course. The red blood cells remained normochromic and normocytic throughout. Reticulocyte counts ranged from 1.3 to 3 per cent.

Leukocytes: During shock there was invariably a neutrophilic leukocytosis varying from 14,900 per cu. mm. with 50 per cent polymorphonuclears and 22 per cent band forms to 45,800 per cu. mm. with 80 per cent polymorphonuclears and 7 per cent band forms. The leukocytosis was an early finding, would persist for the duration of the hypotensive phase, and then subside promptly in the recovery period. During the mild episodes of fluid retention without drop in blood pressure or increase in hematocrit, the white blood cell count either remained normal or at most rose up to 11,600 per cu. mm. Between episodes of shock the white count was normal with 6,000 to 8,000 white cells per cu. mm. but with a mild lymphocytosis of from 38 to 46 per cent. Eosinophilia was absent during the shock periods but from 4 to 9 per cent eosinophils were observed during the recovery period on most but not all occasions. The platelets remained normal in morphology and number at all times.

A bone marrow aspiration on April 10, 1957, two weeks following recovery from an episode of shock, was entirely normal except for an eosinophilia of 6.5 per cent. A repeat marrow aspiration on August 31, 1958, was normal except for a mild plasmacytosis of 3 per cent and hyperplasia of the reticulum cells. Only 2 per cent eosinophils were found in this specimen.

Renal Function. Routine urinalysis remained normal throughout the patient's course. The specific gravity of the urine ranged from 1.030 during oliguric phases to 1.008 during the recovery phases. Microscopic examination revealed no abnormalities at any time except for an occasional hyaline cast during the shock episodes. No proteinuria was ever detected during the asymptomatic stages and urine specimens collected during shock and the immediate recovery period showed only 0 to 1-plus proteinuria. On two occasions the twenty-four-hour urine volume during shock episodes was 200 and 145 cc., and contained only 0.04 and 0.15 gm. protein per total volume, respectively. The day following the first of these shock episodes the urine volume was 2,150 cc. and contained 0.43 gm. protein per total volume.

It is of interest that there was no significant proteinuria in the face of a diffuse and massive increase in capillary permeability. This may have been due in part to decreased renal blood flow and glomerular filtration rate during the shock episodes.

A Fremont-Smith water loading test showed that 877 cc. of the administered 1,200 cc. water load was excreted within the three-hour period, a normal response.

The blood urea nitrogen was normal during asymptomatic periods and immediately preceding shock periods, but would rise to a peak within two to three days following shock to levels varying from 25 to 95 mg. per cent on different occasions. At first the blood urea nitrogen returned to normal levels within about a week following the peak elevation but later in her course it remained slightly elevated (circa 20 mg. per cent) for several months following a severe shock episode. Following the periods of shock the urea clearance was depressed, reaching a recorded low of 41.7 per cent of the average normal

maximal clearance two weeks after one episode when the blood urea nitrogen was 16.9 mg. per cent. A urea clearance test performed during an asymptomatic period on January 9, 1959, just twelve days before her death, was 80 per cent of the average normal maximal clearance, with a blood urea nitrogen of 21 mg. per cent.

Cardiac Function. The heart was entirely normal when the patient was examined prior to her first admission in shock. Figure 4 illustrates the marked electrocardiographic changes which occurred during severe episodes of shock and the reversion toward a normal tracing during the recovery period. The venous pressure was normal during the asymptomatic periods but was noted to be elevated as high as 210 mm. saline during the recovery phase of shock when the administered plasma or albumin returned to the vascular compartment.

Demonstration of Increased Capillary Permeability. The profound loss of plasma from the vascular compartment was demonstrated by observations of four parameters: hematocrit, plasma volume, T-1824 dye disappearance curve and radioactive iodinated serum albumin studies.

Hematocrit: The marked changes in hematocrit have already been discussed and are indicated in Table I and Figures 2 and 7.

Changes in plasma volume: The blood volumes were measured serially during one episode of shock which occurred on November 29, 1957, using T-1824 dye [*5,6*]. The results are indicated in Table II. As noted, even before frank shock, when the maximum drop in plasma volume would be expected, she had already suffered nearly a 50 per cent decrease in the blood volume. The super-normal plasma volume observed in the recovery phase is undoubtedly due to the plasma administered during treatment in the shock phase. The changes in red cell mass are probably partly due to errors in the method and partly due to the large amounts of blood drawn for studies.

Even greater changes in plasma volume were observed during other more severe episodes of shock, but serial determinations were not made in every instance. During the October 8, 1957, episode of shock, for instance, the plasma volume dropped to 1,245 cc. with a calculated normal of 2,846 cc., the patient's dry weight being 69 kg. at that time. Four days later the plasma volume had risen to 3,660 cc. On this occasion no plasma was administered and the only plasma expander used for treatment of the shock phase was 500 cc. of 6 per cent dextran given in isotonic saline solution.

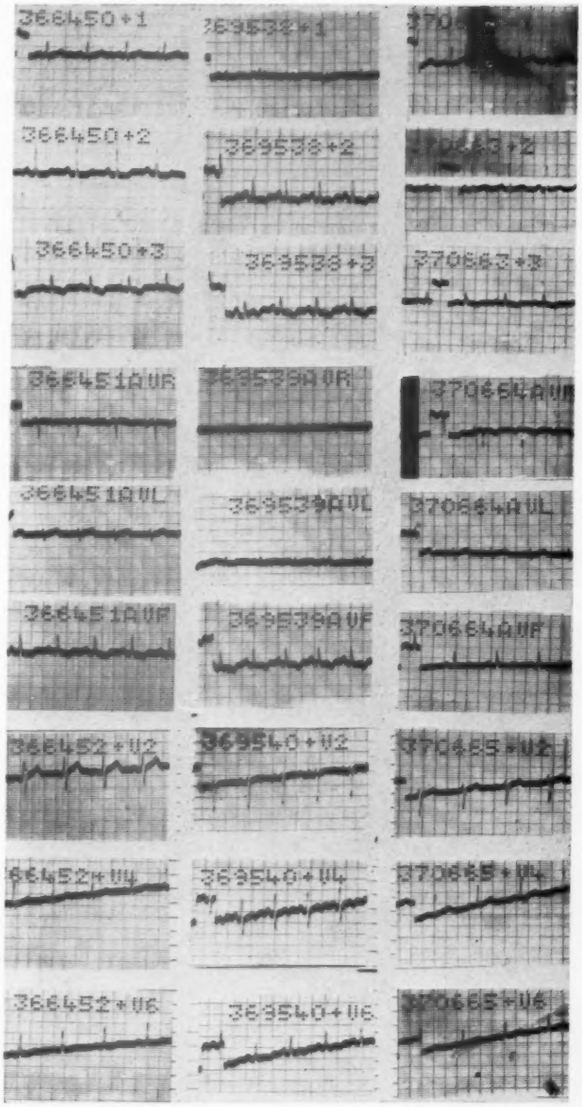


FIG. 4. Typical electrocardiographic changes occurring during an episode of shock. Tracing of March 22, 1958, (*left*) was taken during an asymptomatic phase. There is some residual effect of digitoxin therapy which had been stopped March 11, 1958. Tracing of April 11, 1958, (*center*) was taken during the early recovery phase of an episode of shock which occurred on April 10. Tracing of April 18 (*right*) is after recovery from this episode was complete.

T-1824 dye and radioactive iodinated serum albumin disappearance curves: During an asymptomatic period on November 18, 1957, disappearance curves of intravenously injected T-1824 dye and radioactive iodinated albumin were obtained simultaneously, as shown in Figure 5. The rate of disappearance of the T-1824 was

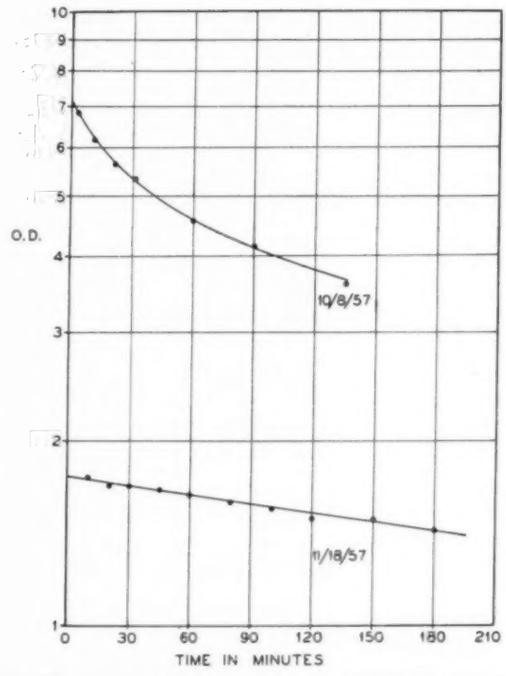


FIG. 5. Plasma disappearance curves of T-1824 dye. The November 18, 1957, T-1824 plasma disappearance curve was obtained during an asymptomatic period, simultaneously with radioactive iodinated serum albumin. The two curves are superimposable, the disappearance rate being 6.2 per cent per hour for T-1824 and 6.3 per cent per hour for RISA. The October 8, 1957, T-1824 disappearance curve was obtained during a period of developing shock. The disappearance rate was approximately 32 per cent in the first hour and 17 per cent in the second hour.

6.2 per cent per hour and the radioactive albumin disappearance rate was 6.3 per cent per hour over a three-hour period. This is a normal rate of disappearance of these compounds [*7*].

On October 8, 1957, during a period of developing shock, the plasma disappearance of T-1824 dye was measured, the dye being administered at the time of the patient's arrival in the Emergency Room when her blood pressure was 60/40 mm. Hg. A more rapid disappearance of the injected dye was noted on this occasion. Since the disappearance curve was curvilinear on a semilogarithmic plot in this instance, the disappearance rates were estimated separately for the first hour and the second hour. A value of approximately 32 per cent was obtained for the first hour and a value of approximately 17 per cent was calculated for the second hour. Both of these disappearance rates are considerably in excess of normal values and are higher than those observed by Noble and Gregerson in shock due to severe burns [*6*].

During the November 29, 1958, episode of shock the T-1824 disappearance rate again was measured, the dye being administered on this occasion while the blood pressure was declining, about forty-five minutes before it became unobtainable. The rate of disappearance was 20 per cent in the first hour at this time.

The rapid disappearance of the T-1824 indicates that there was an increased rate of disappearance of albumin from the vascular compartment.

On November 18, 1957, 0.8 cc. of radioactive iodinated serum albumin (RISA) was injected intravenously during an asymptomatic period. (Fig. 6.) A disappearance curve during the first three hours after the administration of RISA was found to be normal, as already noted. Thereafter blood samples drawn every twelve hours and all twenty-four hour urine specimens were counted for radioactivity. Lugol's solution was given preceding and throughout the radioactive albumin studies to inhibit thyroid uptake and promote excretion of the radioiodine liberated from degraded RISA. The albumin turnover calculations were made in accordance with the method employed by Sterling [*8*] and the results are indicated in Table III. On the morning the test was started, the patient's weight was 65.8 kg. and her serum albumin 4.0 gm. per cent. The half time of albumin turnover of 12.3 days is slightly increased. The total exchangeable albumin pool of 357 gm. is definitely high and is probably due to the additional estimated 80 gm. of exogenous albumin given during treatment of the recent shock episode on November 4, 1957, preceding the radioalbumin study which was started on November 18. The albumin turnover of 5.6 per cent per day is actually low, whereas the turnover rate in gm. per kg. per day of 0.304 is slightly high. The circulating albumin calculated from the data obtained during the first three hours following administration of RISA employing the isotope dilution principle was 120 gm., thus indicating 237 gm. of extravascular albumin. The ratio of the patient's circulating albumin to the total exchangeable albumin pool was 36.3 per cent, the normal distribution being close to 50 per cent [*8*].

The plasma concentration curve of RISA and the per cent retention curve of RISA in the body are shown in Figure 6. The curve of the per cent of RISA retained in the body is based on the assumption that all the radioactivity lost from

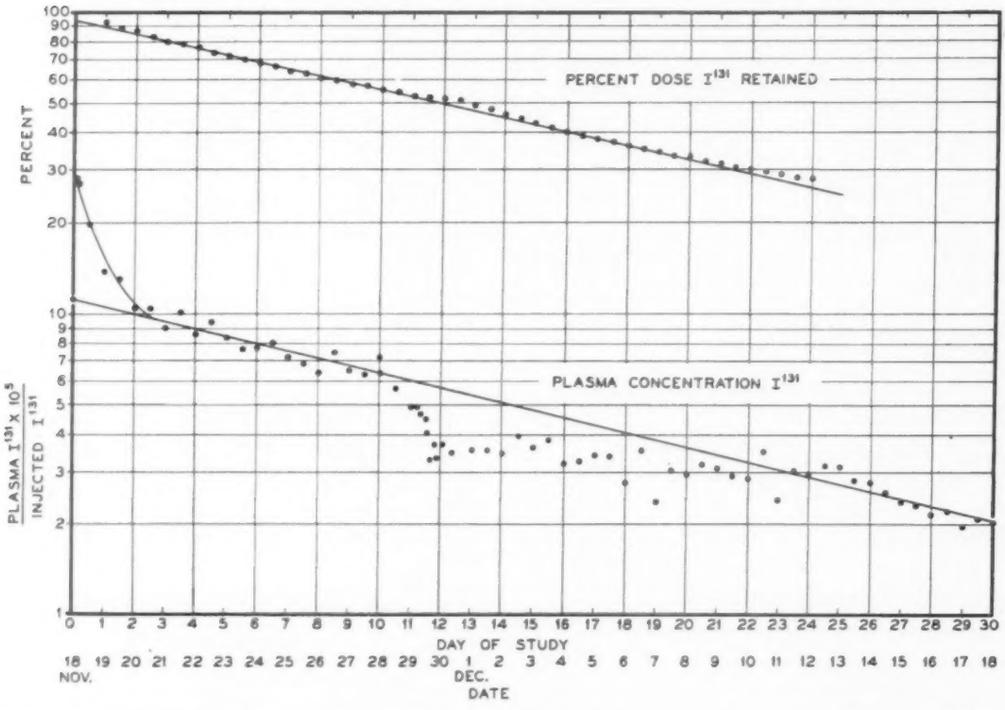


FIG. 6. Radioactive iodinated serum albumin studies. The upper curve shows the per cent of RISA retained in the body. The lower curve shows the plasma concentration of RISA. A shock episode occurred November 29, during which 1,200 cc. of plasma was infused. Discussion in text.

TABLE II

CHANGES OBSERVED IN PATIENT'S PLASMA VOLUME, USING T-1824 DYE, DURING AN EPISODE OF SHOCK

Date	Blood Volume (cc.)	Plasma Volume (cc.)	Red Blood Cell Mass (cc.)	Hematocrit (4% correction for trapped plasma)	Amount of Blood Drawn for Studies (cc.)	Weight (kg.)	Comment
11/18/57	4,422	3,007	1,415	32.0		65.41	Had received 600 cc. plasma plus 100 cc. human albumin during shock episode of 11/5/57; asymptomatic on 11/18/57
11/29/57	3,290	1,578	1,712	52.0	470 between 11/18–11/29	64.68	This study was done during early phase of shock episode, 40 minutes before blood pressure became unobtainable and before therapy was started
11/30/57	3,451	2,050	1,401	40.6	Total 380 between 11/29–12/3	67.31	Had received 1,200 cc. of plasma between 11/29, 11/30 studies; blood pressure stable on 11/30; still oliguric and edematous
12/ 3/57	4,993	3,820	1,173	23.5		65.7	Asymptomatic; edema largely gone, but mild diuresis continued for one week to reach minimum weight on 12/10/58
12/10/57				26.0		61.21	

TABLE III
TURNOVER OF PATIENT'S SERUM ALBUMIN USING I^{131}

Data	Normal Mean and Standard Deviation	Patient
Weight (kg.)	73.2	65.8
Serum albumin (gm. %)	4.4	4.0
Total exchange albumin pool (gm.)	259 ± 40	357.0
Albumin/gm./kg. body weight	3.54 ± 0.61	5.43
Half time albumin turnover (days)	10.5 ± 1.5	12.3
Albumin turnover		
Per cent/day	6.7 ± 0.93	5.6
Gm./day	17.2 ± 2.7	20.0
Gm./kg./day	0.233 ± 0.032	0.304

NOTE: Normal values are from Sterling [8]. Discussion in text.

the body was recovered in the urine collection. That this assumption is valid is supported by the observations that the stools and a gastric aspiration obtained about six hours preceding the shock episode of November 29, 1957, as well as vomitus collected during the shock phase, all showed negligible radioactivity. The small amount of radioactivity lost as a consequence of the blood sampling was disregarded.

The linear portion of the RISA plasma concentration curve is calculated by the method of least squares from the data obtained between day 3 and day 10. This line was then projected to the end of the study. As can be seen from this curve, distribution equilibrium was reached after about the third day. There was a sharp drop in the radioactivity of the plasma during the shock episode of November 29, starting with the infusion of 1,200 cc. of plasma. The curve then returned to follow the pretreatment slope during the recovery phase. We interpret this transient drop in radioactivity in the plasma to be due to immediate dilution of the circulating RISA by the administered, 1,200 cc. of plasma.

The slight rise in the per cent RISA retained in the body following the episode of shock is most reasonably explained by the corresponding phase of oliguria, the patient failing to excrete radioiodine. With onset of the diuretic phase and mobilization of edema fluid, the curve of the per cent RISA retained returns to the previous slope.

It is evident that there was no sudden increase in catabolism of the patient's serum albumin during or prior to shock, since there was no increase in the rate of excretion of RISA.

Other Capillary and Hemodynamic Studies. Observation of conjunctival vessels: The patient's conjunctival vessels were examined by slit lamp by Dr. Robert Landesman both during an asymptomatic intermenstrual phase and during the November 29, 1957, episode of shock. There was no diapedesis or sludging of red cells, and no unusual vasomotion or other abnormalities detected on either occasion.

Demonstration of vasodilating principle: Dr. Silvio Baez of New York University Medical School studied the effect of the patient's plasma obtained in the shock phase and in the asymptomatic phase on the blood pressure of anesthetized rats and also the vasoactive properties of the plasma by the rat mesoappendix method of assay. He found that the patient's shock phase plasma produced severe hypotension which was maximal at two hours following intravenous injection (110 to 30 mm. Hg systolic). Autopsy of one rat made hypotensive in this manner showed ischemia of the gastrointestinal tract and infarction of both upper lobes of the lungs, with hemorrhagic exudate.

The patient's asymptomatic phase plasma produced no significant change in the rat's blood pressure. Both the undiluted shock phase and the asymptomatic phase plasma showed clear-cut vasodilating activity on the rat mesoappendix vessels. The vasodepressor effect of the normotensive plasma disappeared on dilution with saline solution whereas the plasma taken during a shock episode still gave a vasodepressor effect when diluted 1:4 with saline solution.

Plasma Proteins. As has been indicated, the patient's plasma proteins fluctuated markedly during the cyclical episodes of shock, and even in the interim asymptomatic periods the total protein varied as much as 2 gm. per cent for reasons which are not understood. (Fig. 7.) The plasma total protein was usually normal or slightly low during the intermenstrual phase, rose abruptly as the patient went into shock (Fig. 2), fell again during the early recovery phase to subnormal levels, and later in the recovery phase often rose to high normal levels. (Fig. 7.) These fluctuations varied considerably, chiefly as a result of the treatment employed. The highest plasma total protein concentration observed was 7.6 gm. per cent (albumin/globulin, 5.2/2.4), a week after recovery from an

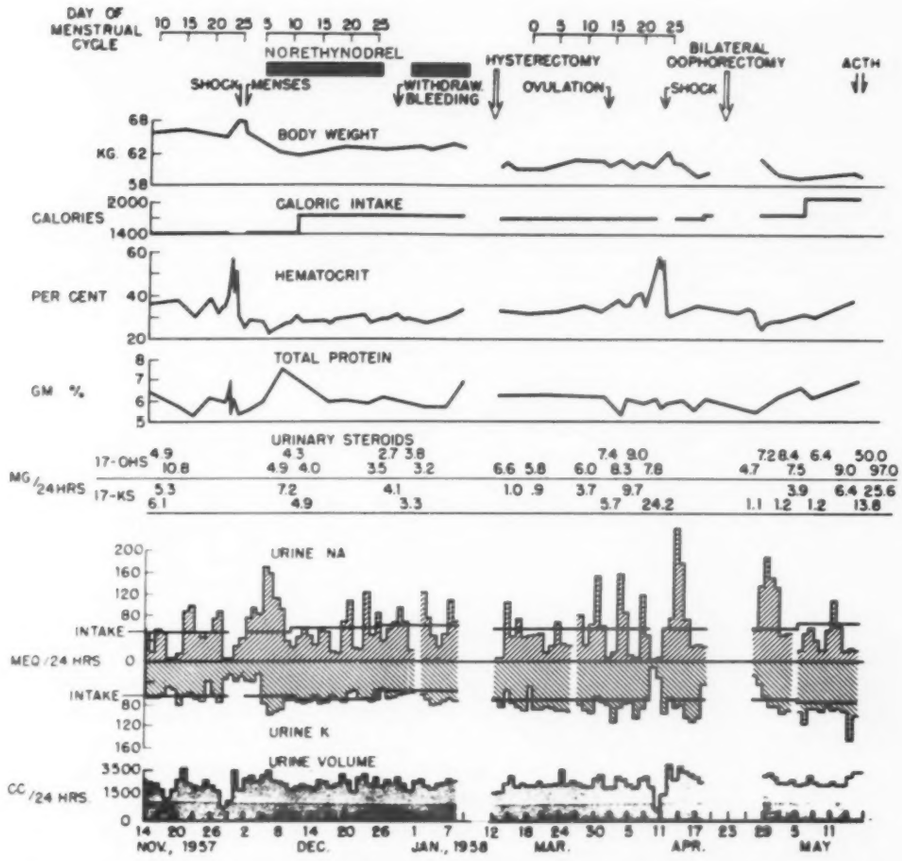


FIG. 7. Metabolic studies conducted while patient was hospitalized in the research pavilion.

episode of shock for which the patient had been treated with 500 cc. of plasma and 100 cc. of salt-poor human albumin. The lowest plasma total protein observed was 2.5 gm. per cent (albumin/globulin, 1.9/0.6) recorded during the early recovery phase of another episode of shock which had been treated solely with large amounts of intravenous fluids, hydrocortisone and levarterenol, but with no plasma or plasma expanders. On other occasions the shifts in the plasma protein were less marked.

During the phase of increased capillary permeability the plasma globulin always fell proportionately with the albumin. Electrophoresis of the plasma proteins during shock showed essentially the same pattern as during the asymptomatic intermenstrual phase, except for dilution of all protein constituents.

Blood fibrinogen during an asymptomatic period was 207 mg. per cent. During a severe shock episode the fibrinogen was 269 mg. per cent and the day following this shock episode it was 325 mg. per cent (normal 250 to 400 mg. per cent).

Immunologic Studies. Demonstration of abnormal gamma globulins: At no time did the patient exhibit an elevated serum globulin, the highest value recorded being 2.5 gm. per cent. On repeated occasions, however, an abnormal fast gamma globulin component was seen on paper, starch gel and Tiselius electrophoresis. (Figs. 8 and 9.) No other abnormalities of the serum proteins were observed on electrophoresis. Dr. Leonhard Korngold of the Sloan-Kettering Institute for Cancer Research tested the patient's serums approximately every two months from November 15, 1957, until the time of her death by the Ouchterlony gel diffusion technic against rabbit antiserum to human fraction 2 serum absorbed with beta globulin and albumin (i.e., antiserum against human gamma globulin). (Fig. 10.) A spur characteristic of an immunologic cross reaction was formed on each occasion, indicating that this patient's serum contained an

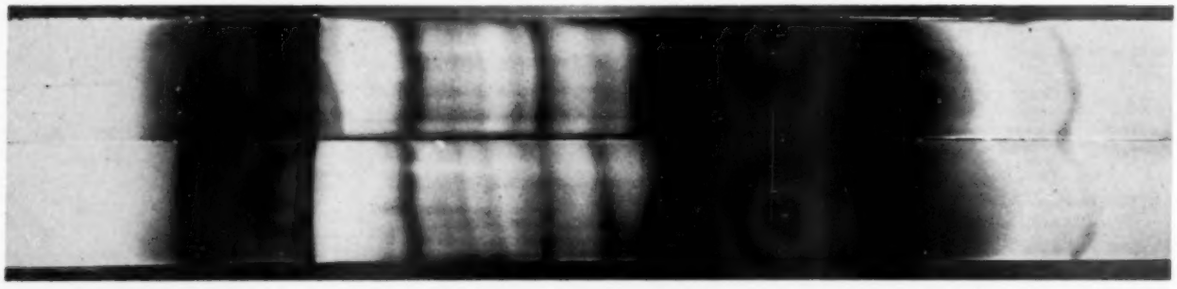
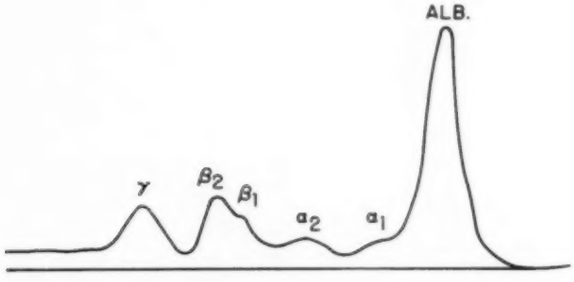


FIG. 8. Starch gel electrophoresis of patient's serum. The *upper* strip shows a normal pattern (albumin at the right, migrating towards the positive pole; gamma globulin at the left, migrating in the opposite direction). The *lower* strip shows the patient's serum proteins. Note the abnormal component in the gamma globulin region; otherwise the patient's proteins by starch gel electrophoresis appear normal.



COMPONENT	CALCULATED MOBILITY		PER CENT	
	PATIENT'S SERUM*	NORMAL SERUM*	PATIENT'S SERUM	NORMAL SERUM
Albumin	6.18	5.7 - 6.2	50.53	63.3
α_1	5.19	4.6 - 5.1	5.88	4.8
α_2	3.98	3.6 - 4.1	4.81	7.6
β_1	3.02	2.8 - 3.2	7.49	12.7
β_2	2.59	2.5 - 2.8	12.30	
γ	1.44	0.8 - 1.3	16.31	11.6

* $\times 10^{-5}$ cm^2 sec^{-1} volt^{-1}

FIG. 9. Boundary electrophoresis of patient's serum (descending limb). Four cubic centimeters of patient's serum diluted to 12 cc. with 0.1 N/2 veronal buffer and dialyzed against the same buffer.

abnormal protein which was antigenically deficient in some of the groupings present in normal proteins [*9*]. This finding was originally thought to be specific for multiple myeloma proteins but has subsequently been observed in serums of patients in whom this disease was not apparent clinically [*10*].

Following the oophorectomy we hoped that this abnormal gamma globulin, presumably an antibody, might disappear, since we had postulated that an ovarian product was the source of antigenic stimulation. However, not only did the patient's serum of June 23, 1958, elicit an abnormal spur formation characteristic of Korngold's myeloma group 2 protein in amounts greater than had been observed previously, but also a new precipitin line pathognomonic of an abnormal macroglobulin had now appeared [*11*]. Dr. Korngold estimated that perhaps three times the normal amount of macroglobulin was present. The patient's serum was not ultracentrifuged, but previous studies have shown excellent correlation between the intensity of the macroglobulin precipitin line on the Ouchterlony plate and the amount quantitatively calculated from ultracentrifugal analysis [*12*]. The precipitin line indicating the abnormal macroglobulin was no longer evident on later determinations, although the line characteristic of "myeloma protein group 2" was repeatedly demonstrated in undiminished concentration in the patient's serum up to and including that drawn the day before her death.

Heparin-precipitable protein: The interesting observation was made that when the patient's heparinized plasma was allowed to stand in the refrigerator for over half an hour a heavy gelatinous flocculent material sank to the bottom of the tube. It was at first suspected that this might be a cryoglobulin but detailed studies showed that it was actually a heparin-precipitable protein [*13*]. Normal human heparinized plasmas drawn for comparison contained small amounts of heparin-precipitable protein but only about a tenth as much as that in the plasma of our patient. The precipitate from our patient's plasma, when separated by centrifugation in the cold, washed with borate buffer and subjected to starch gel electrophoresis, migrated as a very discrete thin band in the mid-albumin region, indicating a protein of unusual purity. An attempt was made to electrophorese the heparin-

precipitable component of normal human plasma in a similar fashion, but the amount obtained was inadequate to provide a discernible band on the starch gel strip.

The significance of the increased heparin-precipitable protein in this patient is not known, but it is noteworthy that heparin-precipitable protein has been found in increased amounts in patients with acute rheumatic fever and in rabbits following an intravenous injection of endotoxin derived from gram-negative bacteria [*13*]. Further, it has been suggested that heparin-precipitable protein may be a precursor to the fibrinoid-like material found in the lumen of various capillaries in the generalized Shwartzman reaction in that "liquoid" (Hoffmann-La Roche sodium polyanetholsulfonate) precipitates the protein from the plasma *in vitro*, and also produces the lesions of the generalized Shwartzman reaction in rabbits when injected intravenously [*14*]. It has been noted by Thomas et al. that washed and redissolved heparin-precipitable protein obtained from rabbits given injections of endotoxin migrated on paper electrophoresis in a manner similar to fibrinogen [*13*]. Our patient's protein migrated on starch gel electrophoresis as a discrete band in the albumin area and was clearly not fibrinogen, which does not diffuse at all through starch gel. Similarly it could not be the macroglobulin demonstrated on the Ouchterlony plate because macroglobulins also fail to diffuse through the starch gel.

Skin and precipitin tests: Skin and precipitin tests were performed with the following in varying concentration in aqueous suspensions, in peanut oil or in both: Pork muscle extract, progesterone, progynon, pregnandiol, estradione, estrone, cholesterol and testosterone. The patient's own intermenstrual vaginal secretion, a homogenate of an endometrial biopsy, and endometrial and ovarian tissue obtained from the frozen surgical specimens were also tested intracutaneously in the patient and for precipitin reactions against both her shock phase and asymptomatic phase serum. Results of all these tests were either completely negative or inconclusive.

Metabolic and Endocrine Studies. Sodium and potassium balance: The patient's weight, caloric intake, sodium and potassium intake, daily urinary volume and urinary excretion of sodium and potassium during her stay on the metabolic pavilion are indicated in Figure 7. Even during the patient's asymptomatic phase the sodium excretion fluctuated considerably, with no apparent correlation with any symptoms and while on a constant diet. The chloride excretion followed the sodium excretion closely and is not charted. The potassium excretion remained fairly constant. Unfortunately the patient was

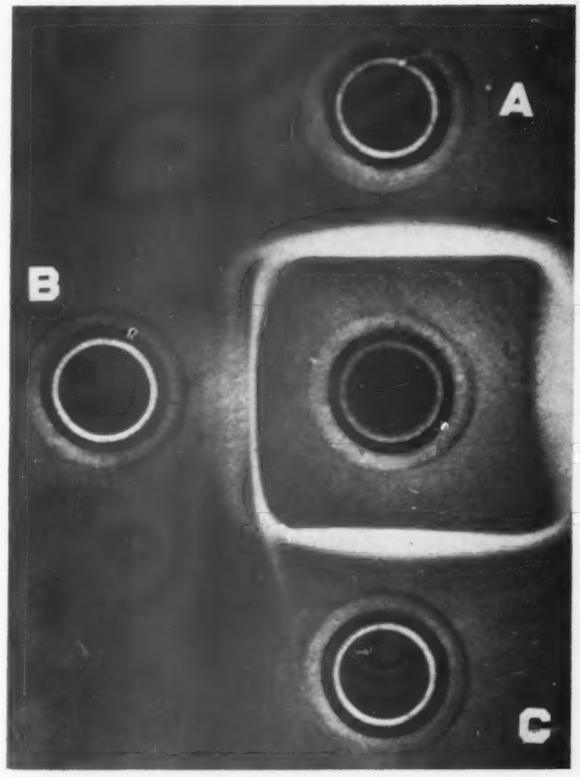


FIG. 10. Demonstration of abnormal serum proteins by Ouchterlony agar diffusion plate. In the center reservoir is rabbit antinormal human gamma globulin; in reservoir A is normal human gamma$_2$ globulin; in reservoir C is group 1 myeloma protein; in reservoir B is the patient's serum diluted 1:50 (serum of July 7, 1958, during an asymptomatic phase). The distinct line between the patient reservoir and closest to the central antibody reservoir is the abnormal "group 2 myeloma" protein. This line is partially fused with the precipitin line of the group 1 myeloma protein, but double spurs can be seen at the intersection of these lines which indicate that each of these "myeloma" proteins contains antigenic groupings which are deficient in the other but will react with antiserum to normal gamma globulin. The broad faint line between the center antibody reservoir and closer to the patient's serum reservoir is her normal gamma globulin. It will be noted that this line is fused with the precipitin line of normal gamma$_2$ globulin from reservoir A. Closest to the patient's reservoir there is a very faint line with its convexity away from the patient reservoir, which, due to its characteristic curvature and location near the patient reservoir, is pathognomonic of an abnormal macroglobulin present in low concentration. (No precipitin line is seen with normal macroglobulin when the test serum is diluted 1:50.)

TABLE IV

NITROGEN, CALCIUM AND PHOSPHORUS BALANCE

Period	Date	Caloric Intake	Intake (gm./24 hours)			Urine Output (gm./24 hr.)			Feces Output (gm./24 hr.)			Balance (gm./24 hr.)		
			N	Ca	Ph	N	Ca	Ph	N	Ca	Ph	N	Ca	Ph
I*	11/16–11/22/57	1,463	10.20	1.021	1.458	9.34	0.133	1.003	1.16	0.771	0.380	−0.30	+0.117	+0.075
II	12/27–12/31/57	1,740	11.00	1.136	1.573	8.96	0.026	0.937	1.35	1.330	0.620	+0.69	−0.220	+0.016
III†	1/ 1– 1/ 7/58	1,740	11.00	1.136	1.573	9.02	0.031	0.773	1.09	1.143	0.566	+0.89	−0.038	+0.234

* A severe shock episode occurred following period I on 11/29/57.

† The patient was taking nor-ethynodrel 30 mg. four times a day during period III and had been taking this compound immediately prior to period II.

not followed for a sufficient length of time before her menstrual cycle was interrupted by drug therapy or operative procedures to reach any definite conclusion about sodium and fluid retention intermenstrually or premenstrually; however, it can be seen in the two instances observed preceding the onset of shock that marked sodium retention did not take place. As would be expected, with the onset of shock the sodium and potassium excretion declined abruptly, along with a decrease in urinary output. This was followed in the recovery phase by a moderate diuresis and natriuresis. The serum electrolytes were consistently normal except for transient mild depression of the bicarbonate during the shock phase and minimal transient elevation of the serum potassium (highest 5.4 mEq./L.) during the early recovery phase.

One five-day and two seven-day nitrogen, calcium and phosphorus balance studies were made during asymptomatic periods, as shown in Table IV. The patient was in slightly negative nitrogen balance during the first period and went into positive nitrogen balance when the caloric intake was raised. Repeated determinations of the serum calcium, phosphorus and alkaline phosphatase were all within normal limits. Urinary excretion of calcium and phosphorus was measured during the patient's stay in the metabolic pavilion. The calcium excretion initially ranged from 108 to 180 mg. per twenty-four hours (average 142 mg. per twenty-four hours) while receiving 1.021 gm. calcium. Following an episode of shock on November 29, 1957, the urinary excretion of calcium fell to levels of from 12 to 56 mg. per twenty-four hours (average 28 mg. per twenty-four hours) while on practically the same calcium intake (1.136 gm.). However, nor-ethynodrel in dosage of 30 mg. four times a day, was coincidently started on December 2, 1957, the first day after the shock episode on which complete urinary collections were resumed. The hypocalciuria persisted for over a month, at which time calcium studies were stopped. These balance periods revealed that the fecal excretion of calcium increased following the shock episode and institution of nor-ethynodrel therapy to more than compensate for the decreased urinary excretion, with resulting over-all negative calcium balance. (Table IV.) There was no diarrhea at this time and no significant alteration in nitrogen or phosphorus balance. The only explanation which comes to mind for the changes in calcium balance in the second two periods is the possibility that they may have been due to nor-ethynodrel therapy.

Vaginal smears and basal body temperature: Vaginal smears were made daily or every other day during the better part of the patient's course, both while in the hospital and while at home, as were daily basal body temperatures. These were reviewed by Dr. Eugene Cohen. The smears and temperature charts invariably showed a normal ovulatory cycle, ovulation occurring at about the fourteenth day of the cycle except during therapy with the 19-nor progestational steroid when there was marked suppression of vaginal cyclical changes; cornification of the vaginal epithelium reached a peak of 60 to 65 per cent before treatment and only about 5 to 10 per cent during treatment with nor-ethynodrel.

Following hysterectomy on March 5, 1958 a normal ovulatory cycle was again observed, as

TABLE V
RESULTS OF ACTH TESTS

Date and Period	Urinary Excretion (mg./24 hr.)		Plasma* (μg. %)
	17 OH-S	17 K-S	17 OH-S
April 1957			
Control day	4.14	...	
1st ACTH day	11.89	14.35	5.40 (8.40)
2nd ACTH day	51.20	29.30	51.00
May 1958			
Control day	8.96	6.40	
1st ACTH day	49.56	13.80	36.10 (38.70)
2nd ACTH day	96.96	25.60	33.30 (43.80)

* Figures in parentheses represent values after therapy with ACTH.

judged by the vaginal smears and basal body temperature. Without knowledge of the temperature chart, Dr. Cohen judged on the basis of the vaginal smears that ovulation occurred on March 31, 1958. The basal body temperature showed a distinct elevation of 0.3°C. on April 1 and this persisted until the next episode of shock on April 10, 1958. Following bilateral oophorectomy on April 21, 1958 the vaginal smear showed typical postmenopausal atrophic changes which persisted until the time of the patient's death.

Pituitary gonadotropin: A modified Klinefelter assay for pituitary gonadotrophin was positive at 6.5 mouse units per twenty-four hours and negative at 13 mouse units per twenty-four hours in November 1957, prior to nor-ethynodrel therapy. The assay was repeatedly negative at all concentrations during the periods of nor-ethynodrel therapy. Following hysterectomy on March 5, 1958 the pituitary gonadotrophin titer was positive at 13 mouse units per twenty-four hours and negative at 52 mouse units per twenty-four hours on March 28, 1958, and negative at all dilutions on April 8, 1958. Following bilateral oophorectomy on April 21, 1958 the pituitary gonadotrophin remained positive consistently at 13 mouse units per twenty-four hours except for a transient elevation to 52 mouse units per twenty-four hours on April 27, 1958.

Adrenal steroids: The urinary excretion of corticosteroids (Porter-Silber; normal, 4 to 12 mg. per twenty-four hours) was measured on over forty occasions at intervals during the patient's course. Values ranging between 2.69 and 12.21 mg. per twenty-four hours were obtained. The values usually fluctuated between 6 and 9 mg. per twenty-four hours, except during the period of nor-ethynodrel therapy when there was a mild depression to about 3.5 mg. per twenty-four hours, only one value below 3 mg. per twenty-four hours being recorded. No significant variation in the corticosteroid excretion which could be correlated with the menstrual cycle or periods of shock was noted, nor was there any significant change following bilateral oophorectomy. The values obtained during the patient's stay on the metabolic pavilion are shown in Fig. 7.

17-ketosteroid excretion (normal, 4 to 12 mg. per twenty-four hours for females): The 17-ketosteroid excretion was in the normal range (4.9 to 7.85 mg. per twenty-four hours) on repeated occasions prior to hysterectomy but thereafter fluctuated widely, both before and after bilateral oophorectomy, from 0.87 to 24.2 mg. per twenty-four hours. During the period between hysterectomy and oophorectomy no correlation was evident between the levels of 17-ketosteroid excretion and the patient's clinical course, or with the sodium or potassium excretion, with one possible exception. A single elevated value of 24.2 mg. per twenty-four hours was obtained when the patient was asymptomatic on the day before she went into shock on April 10, 1958. The steroid excretion was not measured at such a critical juncture on other occasions and this observation was not confirmed. The 17-hydroxy steroid excretion in the same urine specimen was 7.75 mg. per twenty-four hours. Following oophorectomy the 17-ketosteroid excretion was generally lower, four values below 1.19 mg. per twenty-four hours being obtained. The subsequent levels did not exceed 6.4 mg. per twenty-four hours. The values obtained during the patient's stay on the metabolic pavilion are recorded in Figure 7. Unfortunately, the excretion of etiocholanolone and aldosterone was not measured.

Two ACTH stimulation tests were made during asymptomatic periods, one during the early part of her course, the second following bilateral oophorectomy. Forty units of ACTH were infused intravenously in 500 cc. of saline solution over an eight-hour period on each of two successive days. The results are shown in Table v. These ACTH tests were judged to be within normal limits as performed in this laboratory,

except for the high 17-hydroxysteroid excretion value on the second day of stimulation in the second test, which indicates an exaggerated responsiveness of the adrenal cortex to stimulation. The control plasma cortisol value of the second test before the administration of ACTH also is high (normal 4 to 28 μg. per cent), but failed to rise even as high as usual with stimulation. We interpret these tests as showing an essentially normal adrenal response to ACTH stimulation.

Miscellaneous. The plasma ascorbic acid was 1.2 mg. per cent (normal, 0.75 to 1.5 mg. per cent), serum amylase 21 units, serum beta carotene 0.12 mg. per cent (normal, 0.06 to 0.368 mg. per cent). The Mazzini test was negative, the Wassermann test was negative, no porphobilinogen was present in the urine, the Coombs' test was negative, L.E. preparations were negative on two occasions, the stool guaiac was repeatedly negative. The serum bilirubin, thymol turbidity test, cephalin flocculation test and prothrombin time were repeatedly normal except during and for a few days following an episode of severe shock, when there were mild and transient abnormal results. The SGO transaminase on one such occasion (February 13, 1958) rose to 610 units per ml. per minute (normal up to 45 units), the serum bilirubin rose to 1.8 mg. per cent, and the prothrombin time became slightly prolonged. All these tests returned to normal within ten days. Myocardial and skeletal muscular damage may, of course, have contributed to the elevated SGO transaminase. The serum cholesterol on different occasions was 245 mg. per cent, 184 mg. per cent and 240 mg. per cent, with 70 per cent esterified. The basal metabolic rate was plus 1, minus 11 and minus 16 on three occasions. Both oral and intravenous glucose tolerance tests on several occasions were within normal limits, as was the insulin tolerance test. A vitamin A tolerance test showed a normal rise in serum carotene and in vitamin A following an oral dose of vitamin A. The serum iron drawn on December 27, 1957, prior to any surgery was 111 μg. per cent (normal, 90 to 130 μg. per cent), the latent iron binding capacity was 150 μg. per cent and the total iron binding capacity 261 μg. per cent, indicating 42.5 per cent saturation.

Roentgenograms: Roentgenograms of the chest were normal except during the period of acute cardiac failure in February 1958 when marked cardiac enlargement and bilateral pleural effusions were observed. However, subsequent chest roentgenograms were within normal limits. Sinus x-rays, gastrointestinal and small bowel series, barium enema, gallbladder series and intravenous pyelogram were all within normal limits.

Postmortem examination: There was no gross subcutaneous edema and the tissues were dry. No fluid was found in the peritoneal or pleural cavities. The pericardium contained only 50 cc. of clear, yellow, watery fluid. The heart weighed 300 gm., no abnormalities were found. The lungs were dark red, weighing 920 gm. together, and on pressure exuded small quantities of pink fluid. The bronchi appeared normal. The pulmonary arteries as well as all the other vessels were widely patent. The liver was pale brown and weighed 1,630 gm. The biliary ducts appeared normal. The wall of the gallbladder was thickened and had interlacing whitish mucosal lines. The spleen weighed 215 gm. The alimentary tract appeared normal and contained no unusual amount of fluid. The thyroid was normal in size and contained a single 0.8 cm. nodule deep in the left lobe. The pancreas was within normal limits. The adrenals were small, but otherwise appeared normal. The kidneys were pale brown and weighed 240 gm. together. The ureters and bladder were normal in appearance. The ovaries and uterus were absent and no accessory ovarian tissue could be found. The bone, joints and marrow all appeared normal. The lymph nodes throughout the body were normal in size and consistency. A persistent fleshy lobulated thymus which weighed 29.9 gm. was present. The brain weighed 1,290 gm. There was congestion of the pial blood vessels and of the small vessels throughout the cerebral hemispheres. The ventricular system was normal. There was a brownish hemorrhagic discoloration measuring 1.5 cm. across extending anteriorly and posteriorly through most of the pons. There was no softening in this area. The substantia nigra showed less pigmentation than is normal for this age. The pituitary appeared normal except for a round, white mass measuring 0.5 cm. near the infundibulum in the anterior portion.

On microscopic examination the heart showed minimal subendocardial thickening of the left atrium. Small focal areas of fibrous replacement of the myocardium were the only abnormalities noted. The lungs showed focal areas of atelectasis. The capillaries of the alveolar septums were

engorged, and blood and focal areas of hemorrhage were noted in many of the alveoli. The splenic sinusoids were congested with red blood cells and some of the arterioles showed slight hyaline thickening. The liver was normal in appearance. The adrenal cortex was thin. The zona glomerulosa was finely vacuolated, sparse vacuoles were seen in the zona fasciculata, the zona reticularis was somewhat atrophic. The cells near the medullae contained some brown-yellow pigment. The thyroid nodule contained essentially normal thyroid tissue.

The cortex of the kidneys contained many small, irregular scars (Fig. 11), the site of extensive atrophy and distortion of tubules associated with marked glomerular and periglomerular fibrosis, and in some areas deposits of calcium within the tubules or interstitial tissue. Many of the scars were devoid of inflammatory cells but some contained moderate numbers of lymphocytes. The remaining glomeruli appeared to be essentially normal, nor was there evidence of significant arterial fibrosis or other change in the vessels.

The thymus contained well formed Hassal bodies. The gallbladder showed evidence of chronic cholecystitis and cholesterosis. The posterior pituitary appeared normal. In the anterior pituitary there was a small round tumor mass comprised of columnar-like chromophobic cells arranged in layers about fine vascular connective tissue strands forming tiny sinuses. Uncompromised pituitary tissue was present around the adenoma. Bone marrow from the vertebras, sternum, iliac crest and rib was normoplastic. There was mild granulocytic hyperplasia. Erythropoietic cells and megakaryocytes were present in normal numbers and there was no excess of plasma cells or eosinophils.

Fluorescent Antibody Stain of Kidney for Localized Gamma Globulin. Goat antiserum to human gamma globulin was used. The goat gamma globulin was separated by alcohol fractionation, coupled with fluorescein isothiocyanate, and absorbed with lyophilized mouse and rat liver powder [*15*]. Fresh frozen sections of the patient's kidney were then stained with this absorbed, fluorescent-labeled antibody against normal human gamma globulin. There was no fluorescence of any of the glomeruli or small vessels. The only specific fluorescence that was seen consisted of a few scattered clumps of material which were shown to lie within a few of the kidney tubules and thus were identified as tubular protein casts which contained some gamma globulin.

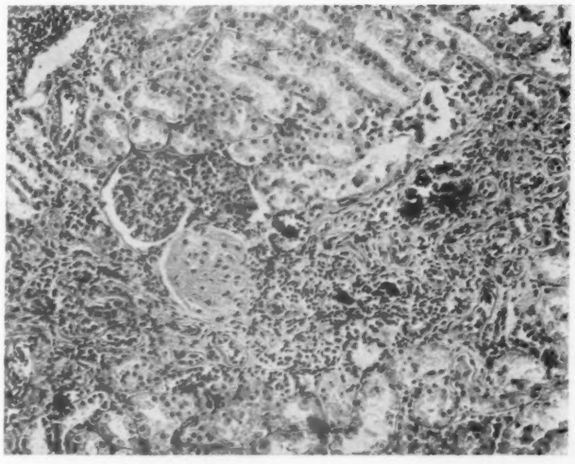


FIG. 11. Typical small scar in cortex of kidney. Note atrophy and distortion of tubules, focal deposits of calcium, glomerular and interstitial fibrosis, and virtual absence of inflammatory cells. Hematoxylin and eosin stain × 140.

Electron Microscopy of Kidney. The kidney sections were not fixed for electron microscopy until six hours after the patient had died, and hence it was not immediately certain which of the observed changes from the normal were due to autolysis. As is shown in Figure 12, the basement membrane of the glomerular capillaries was irregularly and moderately thickened in some areas while in others it appeared to be fairly normal. There was distortion of the foot processes of the epithelial cells in many areas, in others these were intact. Both the epithelial and the endothelial cells appeared swollen and contained increased numbers of intracytoplasmic vacuoles and vesicles. (Here postmortem changes cannot be excluded as a reason for these findings.) The specimen obtained for study unfortunately was from one of the scarred portions of the cortex where fibrosis and obliteration of the glomerular tuft were common. The changes observed were considered to be of a non-specific nature.

The final anatomic diagnoses were: (1) periodic hypovolemic shock of undetermined etiology; (2) renal fibrosis and calcification probably secondary to ischemic destruction of nephrons; (3) passive hyperemia of lungs and spleen; (4) surgical absence of uterus, fallopian tubes and ovaries; (5) persistent thymus; (6) chromophobe adenoma of pituitary; (7) atrophy of the adrenal glands (presumably second-

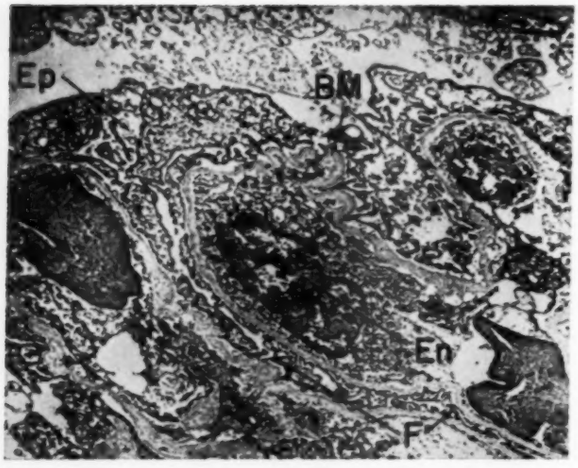


FIG. 12. Electron micrograph of a portion of a glomerulus from one of the focal scars in the cortex. BM = capillary basement membrane, which shows irregularity and focal thickening. Ep = epithelial cell, which is swollen. En = swollen endothelial cell which fills capillary lumen. F = foot processes (podocytes) of epithelial cell, which appear distorted in some areas. (Six hour postmortem the kidney was fixed in buffered osmium tetroxide. Many vacuoles, vesicles and general loss of the finer cytoplasmic detail are probably due to postmortem autolysis.)

ary to exogenous corticosteroids); (8) adenoma of the thyroid; (9) chronic cholecystitis and cholesterosis of gallbladder; and (10) absence of pigment in substantia nigra.

COMMENTS

The case, then, is that of a thirty-four year old woman who appeared to be entirely healthy but who periodically would rather suddenly have an extreme generalized increase of the permeability of her capillaries resulting in hemoconcentration and shock of such marked degree that her vital organs were severely damaged. In one such episode of shock she suddenly died, presumably because of cardiac arrest due to prolonged hypotension and hypoxia, as autopsy failed to reveal any other cause.

Between these periodic episodes of shock she was almost entirely asymptomatic and was able to lead an active normal life as mother and housewife. In fact, the only abnormalities which were demonstrable during these asymptomatic phases were a minimal eosinophilia and lymphocytosis and a persistent abnormal gamma globulin. Because of these findings and the nature of her otherwise baffling shock episodes, it seemed plausible to consider that the latter were due to some type of hypersensitivity reaction.

Particularly striking was the fact that these episodes of shock almost invariably occurred in the premenstrual phase of her menstrual cycle. This observation, coupled with our inability to demonstrate any other apparent cause, led us to perform a hysterectomy and then an oophorectomy in the hope of removing an endogenous allergen which might be produced by one of these organs, and thereby prevent further shock episodes. For about four months following the oophorectomy she had no further attacks, then the shock episodes recurred. Although a hypersensitivity phenomenon still seemed to be the most plausible hypothesis, we were now at a loss to incriminate even circumstantially any suspicious antigen. Several of the attacks, it is true, occurred shortly after the development of an infection of the respiratory tract, usually transmitted by a member of her family; consequently a viral antigen as a precipitating cause was postulated and still cannot be excluded. However, sometimes it was difficult to be sure that she did in fact have an infection of the upper respiratory tract, as in some instances the only suggestive symptom was rhinorrhea. This could have represented a vasomotor phenomenon rather than being of infectious origin. Furthermore, on other occasions there were no symptoms to suggest an infection of the respiratory tract. The postmortem findings shed little light on the etiology of her shock episodes.

We have been able to find only a single case in the literature which seems comparable to the one presented therein [*16*]. Few details are given. Observations of the blood pressure and hematocrit are not mentioned, but it is noted that the episodes of edema occurred premenstrually and that the blood constituents increased in concentration by as much as 10 or 12 per cent. As our patient's hematocrit sometimes more than doubled during a shock episode, it would seem that she had a much more severe form of the disorder. The patient previously recorded in the literature also had a hysterectomy and later an oophorectomy (although only unilateral) without alteration in her course. She was then given a crude preparation of chorionic gonadotrophin available at that time, following which it was stated that her cyclical episodes of edema stopped.

Cyclical edema occurs almost exclusively in adult women and the edema is most often related to the menstrual cycle, usually occurring in the immediate premenstrual period [*17*].

Thorn has reviewed the various factors thought to be responsible for the cyclical episodes of edema [*17*], among which the most important are: psychological factors, salt-retaining properties of the female sex hormones, secondary hyperaldosteronism, the possible influence of ADH and the contributing influence of organic disease. He mentioned the phenomenon of increased capillary permeability as a possible mechanism in causing retention of fluid but stated that with present technics it is difficult to prove conclusively that such alteration in permeability actually takes place.

The outstanding feature in our patient was, of course, the cyclical episodes of shock. In the milder episodes, however, the only manifestation was fluid retention as evidenced by a sudden weight gain and generalized swelling which was most noticeable as a tightness of the skin of the extremities and puffiness of the face. She sometimes gained as much as 5 kg. in less than twenty-four hours without any fall in blood pressure. During the episodes which were observed in the hospital, when it was possible to measure her fluid intake and output accurately, it quickly became obvious that the degree of edema was dependent on how much fluid she drank or was given parenterally during the period of increased capillary permeability. Balance studies failed to show any significant salt retention as an important factor in the initial phases of the development of these shock episodes.

Our studies of the changes in the hematocrit and the blood volume, as well as the T-1824 dye and radioactive albumin curves, demonstrate beyond reasonable doubt that our patient's cyclical episodes of fluid retention and in some instances of frank shock were due to a sudden and pronounced increase in capillary permeability. This allowed loss of circulating protein and fluid from the vascular compartment into the tissue, with resulting marked contraction of the plasma volume and consequent hemoconcentration and severe hypotension. The possible alternative explanations for the production of a shock state seem to us to have been excluded. The radioactive iodinated serum albumin studies ruled out sudden protein catabolism as a possible cause of shock. The albumin turnover rate was essentially normal if one takes into consideration the increased size of the total exchangeable albumin pool as a consequence of the exogenous albumin employed in therapy. The shock episodes developed far too rapidly for an abrupt breakdown in protein anabolism to be responsible. Another explanation for the shock would be a transient failure of the lymphatic system normally responsible for returning the serum proteins to the circulation. This seems to us to be highly unlikely for two reasons. First, it is hard to conceive of a reaction which would result in a disruption of the lymphatic mechanisms responsible for homeostasis, and to our knowledge such an occurrence has never been demonstrated. Secondly, the rapidity of disappearance of T-1824 dye from the circulation (32 per cent in one hour in one instance) strongly supports the postulate of a primary capillary lesion rather than decompensation of the lymphatic system. It had been planned to introduce Southey tubes to sample the edema fluid during the shock episode in which radioactive albumin had been given, but insufficient edema developed in accessible areas during this particular episode. Catheterization of the thoracic duct was considered as a means of sampling the lymph but this idea was abandoned because of possible serious sequelae.

The reason for the sudden marked alteration in capillary permeability is unknown, as is the reason for its consistent occurrence during the premenstrual phase of her menstrual cycle. Changes in capillary permeability and vasomotor activity during the menstrual cycle have been noted in normal subjects. Hechter, estimating capillary permeability in castrated rats by the intensity of coloring following administration of trypan blue, found that estrogens increased the permeability of the uterine and vaginal capillaries [*18*]. He believed that the effects of the estrogen were localized to these capillaries and there was no significant alterations in the somatic vasculature. However, other workers have demonstrated beyond doubt that the effect of the sex steroids on the capillaries is more generalized. Camurri, using adult castrated rabbits, found that estrogen and testosterone increased while progesterone decreased capillary permeability [*19*]. Brewer, using the negative pressure method for demonstrating ease of capillary hemorrhage, found that during the immediate premenstrual phase and on the first day of menstruation the capillaries are more fragile than during the remainder of the cycle [*20*]. Russo studied the menstrual variations of capillary permeability in twenty normal women by producing venous stasis in one arm with a sphygmomanometer cuff

for thirty minutes and then comparing the hematocrit and protein loss in samples of venous blood from the cuffed and uncuffed arms [*21*]. Using the second day of the menstrual cycle as a base line, he found that there was a diminution of capillary permeability on the twelfth day of the cycle and an increase on the twenty-first day.

Aside from these studies on variations in capillary permeability during the menstrual cycle a wide variety of systemic disorders have been noted to bear a relation to a particular phase of the menstrual cycle [*22*]. Of possible pertinence to the patient under discussion are some of the following observations. Hansen-Pruss studied the serum of four young women with hayfever at varying phases of their menstrual cycle utilizing the passive sensitization (Prausnitz-Küstner) technic in non-allergic subjects [*23*]. He found that the largest reactions were obtained with serum drawn on the last day of menstruation and concluded that the highest reagin titer occurred at this time. In a study of fifty women who had acute poliomyelitis, Weinstein found that 78 per cent had the onset of symptoms from five days before to four days after the onset of menses [*24*]. Dowling observed that in 77 per cent of female patients who were chilled and given an infectious secretion during the middle third of the menstrual cycle colds developed, as opposed to 28 to 30 per cent similarly treated who were challenged during the first or last third of the cycle [*25*]. In an interesting study McKinnon and McKinnon reported that of forty-seven women who died of suicide, accident or disease, forty-five died in the luteal phase of the menstrual cycle [*26*]. The cyclical occurrence of purpura in association with the menses is well known [*27*] and we have observed several such cases at The New York Hospital. This intermittent purpura is due to thrombocytopenia and may be associated with lymphocytosis and eosinophilia. Fever and nausea may accompany the purpura but edema does not develop. The mechanism is obscure, having variously been suggested to be due to allergic factors, altered endocrine function, or enhanced thrombocytolytic activity by the spleen occurring premenstrually. Our patient never exhibited any hemorrhagic manifestations during the episodes of shock or at any other time. No petechiae were ever observed despite blood pressure recordings as frequently as every few minutes during the shock periods. A Rumpel-Leede test during a shock episode was negative. The platelets were always present in normal amounts, even during the periods of shock. Hemostasis following venopuncture was always prompt and complete, and the blood clotted promptly with adequate retraction of the clot. Furthermore, direct examination of the conjunctival vessels by slit lamp during an attack failed to reveal any diapedesis of red blood cells. It would thus seem that our patient was suffering from a malady quite different from premenstrual purpura and probably bearing little relation to this interesting entity except that both may represent some type of immune reaction, resulting in platelet damage in the one instance and in the other resulting in damage to the vascular endothelium.

The hypothesis that the patient's episodes of shock might be due to an allergic reaction to endogenous ovarian hormones had to be discarded in view of her subsequent course following oophorectomy. She did exhibit some of the features commonly attributed to allergy to endogenous sex steroids including premenstrual fever, edema, nausea and vomiting, and vasomotor rhinitis [*28–30*]. However, in the literature on the subject we were unable to find a similar case in which development of frank shock occurred. The usual means of detecting sensitivity towards endogenous sex steroids is by cutaneous testing with hormones dissolved in various oily solutions or else in the patient's own serum. As has been noted, our patient failed to show any definitely positive skin or precipitin tests to a variety of steroids. In any case it is difficult to reconcile accepted immunologic concepts with known facts about ovarian physiology and hormone production in support of the thesis of allergy to endogenous ovarian steroids. Our patient had a perfectly normal menstrual cycle as judged by vaginal smears and basal body temperatures, with ovulation occurring about the fourteenth day and the menstrual flow appearing usually on the twenty-sixth to twenty-eighth day. Progesterone effect was obvious on the vaginal smears after the fourteenth day and circulating progesterone must have been present in good concentration for at least a week before any symptoms of impending shock developed. Estrogen production was high, of course, for an even longer period. Under these circumstances it is hard to see how allergy could suddenly develop to these hormones or their breakdown products. However, we cannot definitely exclude the possibility that an unidentified steroid metabolite

was in some manner affecting capillary permeability, either directly or through an allergic mechanism.

Nevertheless, it seems most probable that the physiologic changes of the patient's menstrual cycle were not in themselves primarily responsible for the increased capillary permeability but in some ill defined way exerted a powerful modifying influence, unveiling an underlying disease process, so that the shock episodes were prone to occur premenstrually. As we have already pointed out the correlation seemed to us to be too striking to be merely fortuitous.

There remains the question of what underlying disease the patient had. It seems possible that the hypersensitivity reaction could have been due either to an autoimmune phenomenon or to an unidentified foreign antigen such as food or a virus. The eosinophilia and especially the persistent abnormal gamma globulin constituted the major objective laboratory evidence in favor of an immune reaction. At autopsy, anatomical evidence of generalized vascular changes was absent. It had been anticipated that fibrinoid deposition about the small vessels might be found in view of the demonstration of the heparin-precipitable protein during life [*31*]. However, such was not the case.

It seems likely that the small scars in the center of the kidney were secondary to the repeated ischemic insults and not the result of the primary renal disease. Similar renal lesions have been observed in a patient who died following repeated attacks of paroxysmal hemoglobinuria [*32,33*]. The fact that our patient's glomeruli failed to stain with fluorescent-labeled anti-human globulin is further evidence that this was not the usual membranous glomerulonephritis, as Mellors et al. found this to be quite a constant finding in allergic nephritides [*15*].

The absence of detectable structural changes in the patient's capillaries, which can reasonably be correlated with the profound capillary leakage during life, might at first seem surprising. However, one may recall that the relationship of capillary structure to edema in acute glomerulonephritis has not been elucidated and that the full blown nephrotic syndrome may occur clinically with rather minimal morphological changes in the glomeruli even on electron microscopy [*34,35*].

The calcium salts precipitated in the kidney were an unexpected finding. It seems likely that this degree of nephrocalcinosis was also caused in some way by the repeated insults to the kidney during the shock episodes, with tubular damage and precipitation of calcium salts.

There is no evidence that the chromophobe adenoma of the pituitary played any functional role in this patient. On the other hand, in view of our ignorance about the causation of the increased capillary permeability it is not possible entirely to dismiss this finding. The significance of the absence of pigment of the substantia nigra is not known as the patient certainly was not an albino nor did she ever have any symptoms suggestive of Parkinsonism. Experimentally, decrease in pigmentation of the substantia nigra has been observed when this tissue is perfused *in vitro* with adrenalin [*36*]. It will be recalled that large doses of levarterenol were used repeatedly in the treatment of the various shock episodes. Despite multiple marrow samples, at autopsy no plasmacytosis or other abnormal cells were found, and it seems quite definite that she did not have multiple myeloma or any other malignant disease as a cause for the abnormal globulin.

It is apparent that our understanding of this unusual patient is far from complete. It hardly seems conceivable that this case could be truly unique. We hope that some of the recorded observations on our patient may assist in diagnosis and provide clues towards an understanding of the basic disorder in subsequent patients.

SUMMARY

A young woman is described who periodically and inexplicably suffered a sudden phenomenal loss of plasma from her vascular bed and in whom hypovolemia and shock developed. The major episodes of increased capillary permeability usually occurred in the premenstrual period; however, identical episodes continued to occur in irregular fashion following removal of her uterus and ovaries. The disastrous consequences of this sudden increase in capillary permeability, which finally resulted in her death, are described in detail. The underlying reason for the sudden changes in capillary permeability in this patient is not known.

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The Relation of Emotional State to Renal Excretion of Water and Electrolytes in Patients with Congestive Heart Failure*

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An association between stress in life situations and variations in urinary volume has long been known. In 1924 MacKeith [*1*] reported that tension preparatory to running a race was associated with inhibition of urinary output similar to that which occurred during the actual race. The following year Mohr [*2*] published observations demonstrating diuresis during anxiety. These studies suggested that stimuli with emotional significance might give rise either to an increase or to a decrease in renal excretion.

In more recent studies Chambers and Reiser [*3*] presented correlations between stress in life situations and the onset of congestive failure in subjects with cardiac disease. They noted two types of situations to be of special importance in the precipitation of failure. The first included events which aroused feelings of rage and frustration. The hemodynamic changes associated with anger made the response of this group of subjects readily understandable. However, they offered no hemodynamic explanation for the response of the second and larger group of subjects, namely those in whom the events that caused stress prompted feelings of rejection and loss of security.

Schottstaedt, Grace and Wolff [*4*], working with healthy human subjects, demonstrated a retention of sodium and water in situations of tension or discouragement followed by a diuresis of water during subsequent periods of relaxation. Diuresis of water and sodium was observed in situations characterized by excitement, apprehension or anger, confirming the observations of Hinkle, Edwards and Wolf [*5*] on diabetic and non-diabetic subjects during periods of anxiety and hostility. The present study, undertaken under precisely controlled circumstances on a metabolic ward, was designed to explore the possible pertinence of emotional states with their attendant alterations in renal excretion to the state of compensation of the cardiac patient.

METHOD OF STUDY

Eight male subjects were hospitalized on a metabolic ward for periods ranging from fourteen to forty-five days. All of them had been under treatment because of an episode of congestive heart failure and all but one were well compensated at the time the study was started. Only one who had severe problems at home requested early discharge, and therefore could be studied for only fourteen days. Renal function as reflected by urinalysis, blood urea nitrogen and phenolsulfonphthalein excretion remained good in all of these patients. Each patient was carefully studied from the standpoint of emotional development, life experience, attitudes, aspirations, values and vulnerabilities.

The basis of cardiac decompensation is listed in Table 1, with the age of each patient.

The patients were digitalized and given diuretics prior to the study to achieve compensation. Sodium intake was carefully maintained at a constant daily level for each subject, the intake ranging from 1,000 mg. to 2,000 mg. per day. Fluid intake also was regulated. The patients were weighed daily and the body and environmental temperatures were recorded. The urine output was recorded and samples analyzed

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TABLE I

Case No.	Age (yr.)	Type of Illness
I	44	Rheumatic heart disease
II	45	Hypertensive heart disease
III	63	Arteriosclerotic heart disease and leutic aneurysm
IV	50	Cor pulmonale
V	48	Arteriosclerotic heart disease, with multiple myocardial infarctions
VI	43	Hypertensive heart disease
VII	42	Hypertensive heart disease
VIII	45	Arteriosclerotic heart disease with angina

for sodium and potassium. Twelve-hour specimens were collected except during periods of special study when hourly samples were obtained. The time of urine collection was recorded by the patient and verified by the ward nurse.

A record was maintained of activities, visitors, events, reading material, relationship with other patients, and attitudes toward ward personnel. In addition, each patient was visited at least twice each day for approximately one hour to discuss symptoms, and other preoccupations including fantasies, dreams, domestic problems and events on the ward. The patients usually welcomed these discussions. Often they were supplemented by interviews with relatives. Through such verbal statements and careful observation of general behavior and facial expressions, evaluations were made of predominant emotional tone during each twelve-hour collection period. When disagreements occurred in the evaluations of emotional tone made by the two investigators, the period has been listed as "mixed emotional state," no attempt being made to determine which investigator was "right." There were no disagreements between the two investigators in evaluating periods listed as being associated predominantly with anger, apprehension, tension or depression or as predominantly tranquil.

On mornings in which special studies were to be made, hourly specimens of urine were collected. The volume of fluid intake and the time of its consumption were regulated according to a schedule. Posture and bodily activity were controlled: From 9 to 10 A.M., the patient remained in the sitting position, either reading or listening to the radio. From 11 to 12 A.M., ad lib activity was allowed. In all instances, the hour from 10 to 11 A.M. was used for special studies. During some of these periods the subjects were encouraged and reassured. Other periods were devoted to "stressful" interviews in which an event or situation with special meaning was explored. Reactions including verbal response, facial expressions, muscle tightness and alterations in blood pressure and pulse during the interview were carefully noted. During a third group of periods, concentration was maintained by means of arithmetic problems, which the patient solved while in the supine position. The contribution of body position and muscular activity to excretory pattern was evaluated by studies of renal excretion during periods of walking, sitting and lying supine. The periods of lying in the supine position served as a control for the interview periods.

The appraisal of the patient's behavior, attitudes and emotional status made daily was kept scrupulously separate from and not correlated with the laboratory data until completion of the study on each patient. Prior to correlation of the data, attitudes and emotional reactions characterized by a general state of excitement, such as anger or apprehension, were separated from those characterized by a general state of inhibition, such as tension, depression or feelings of being overwhelmed.

RESULTS

In Figure 1 the day-to-day emotional reactions of each patient during the period of hospitalization on the metabolic ward are illustrated. The data are listed under the general categories of excitement and inhibition.

INHIBITORY STATES

Tension and Depression. These patients with heart disease were highly sensitive to any suggestion of an unfavorable prognosis. Moreover, since their illness usually aggravated family and financial problems, many of them suffered more or less prolonged periods of tension and depression. Such a state was associated with a significant decrease of urinary sodium excretion, as shown in Table II. Although all patients showed a decrease in sodium excretion, the level of significance was first calculated omitting three patients (Cases V, VI and VIII), and then recalculated including them in order to avoid errors in sampling. Two patients (Cases V and VIII) each had but a single observation period during which they reported feelings of tension or depression. One patient (Case VI) showed a consistently low sodium output during periods of tranquility so that a marked decrease in excretion was not possible.

The changes in urinary sodium excretion associated with feelings of tension and depression were paralleled by decreases in urinary volume, although these changes were not as marked. Table III contains the data on the volume of urine in the same patients and for the same periods of study as were used in Table II.

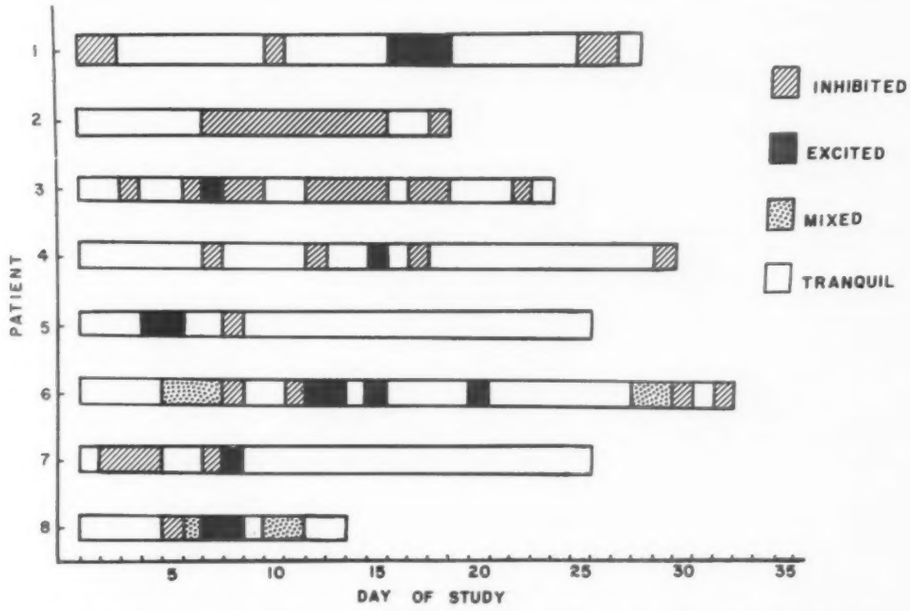


FIG. 1. Emotional states of patients during hospitalization on a metabolic ward.

TABLE II

TOTAL SODIUM EXCRETION IN MEQ. DURING TWELVE-HOUR PERIODS IN COMPENSATED CARDIAC PATIENTS ON CONSTANT WATER AND ELECTROLYTE REGIMEN

Case No.	Tranquil $\bar{x}$	Range	No. of Observations	Tense or Depressed $\bar{y}$	Range	No. of Observations	$D = \bar{y} - \bar{x}$
I	20.5	15.7–24.0	12	12.7	8.9–17.7	5	−7.8
II	30.5	22.6–44.0	4	10.1	4.5–17.9	10	−20.4
III	29.0	14.0–55.0	7	11.0	5.0–15.0	11	−18.0
IV	14.6	9.0–21.5	18	7.3	5.0–10.5	4	−7.3
VII	36.3	21.5–54.6	16	13.7	9.5–17.7	4	−22.6
For five subjects: $\bar{D} \pm SD_D = 15.22 \pm \sqrt{52.7}$					$t = 5.92$	$p < .01$	
V	49.3	40.8–64.2	23	33.9	...	1	−15.4
VI	3.6	1.9– 7.5	8	2.6	2.0– 2.9	4	−1.0
VIII	42.2	24.1–51.3	6	8.5	...	1	−33.7
For eight subjects: $\bar{D} \pm SD_D = 15.78 \pm \sqrt{106.9}$					$t = 4.32$	$p < .01$	

NOTE: In Tables II through IX $\bar{D}$ is the mean difference, SD_D is the standard deviation of the differences, t is the test of significance, and p is the statement of probability. $\bar{x}$ is the mean of observations during tranquil periods, $\bar{y}$ is the mean of observation during inhibitory or excitatory states.

Changes in urinary potassium excretion observed in association with feelings of tension and depression were minor compared to the marked decrease noted in sodium output. However, these changes were also in the downward direction. (Table IV.)

In Table V nocturnal sodium excretion rates for these patients are recorded. There was a significant decrease in urinary sodium during nights when the emotional state of the patient was predominantly tension or depression.

In Table VI a consistent although moderate

TABLE III

TOTAL URINARY VOLUME IN CC. DURING TWELVE-HOUR DAYTIME PERIODS IN COMPENSATED CARDIAC PATIENTS ON CONSTANT WATER AND ELECTROLYTE REGIMEN

Case No.	Tranquil $\bar{x}$	Range	No. of Observations	Tense or Depressed $\bar{y}$	Range	No. of Observations	$D = \bar{y} - \bar{x}$
I	608	460–775	12	557	389–708	5	−51
II	1471	1100–1884	4	1250	400–1662	10	−221
III	1185	1005–1330	7	1001	815–1175	11	−184
IV	1417	875–1965	18	743	620–983	6	−674
VII	627	445–783	16	460	425–490	4	−167
For five subjects: $\bar{D} \pm SD_D = 259.4 \pm \sqrt{71{,}773}$					$t = 2.17$	$p > 0.05$	
VI	1268	1057–1885	23	915	...	1	−353
VI	507	382–870	8	631	410–890	4	+124
VIII	1487	1270–1995	6	900	...	1	−587
For eight subjects: $\bar{D} \pm SD_D = 264 \pm \sqrt{66{,}167}$					$t = 2.90$	$p < 0.02$	

TABLE IV

TOTAL POTASSIUM EXCRETION IN MEQ. DURING TWELVE-HOUR DAYTIME PERIODS IN COMPENSATED CARDIAC PATIENTS ON CONSTANT WATER AND ELECTROLYTE REGIMEN

Case No.	Tranquil $\bar{x}$	Range	No. of Observations	Tense or Depressed $\bar{y}$	Range	No. of Observations	$D = \bar{y} - \bar{x}$
I	27.2	18.4–33.8	12	27.4	18.3–33.2	5	+0.2
II	39.9	21.2–53.9	4	35.4	22.5–51.2	10	−4.5
III	36.6	29.0–42.0	7	35.0	28.0–41.0	11	−1.6
IV	30.4	18.1–45.1	18	26.4	22.8–31.9	4	−4.0
VII	41.7	31.2–53.0	16	35.6	29.0–44.3	4	−6.1
For five subjects: $\bar{D} \pm SD_D = 3.2 \pm \sqrt{6.19}$					$t = 2.88$	$p < 0.05$	
V	41.5	36.9–47.9	23	37.8	...	1	−3.7
VI	24.6	17.8–31.6	8	29.5	22.5–43.6	4	+4.9
VIII	43.4	28.0–54.9	6	21.9	...	1	−21.4
For eight subjects: $\bar{D} \pm SD_D = 4.5 \pm \sqrt{51.9}$					$t = 1.78$	$p > 0.05$	

reduction of urinary volume during nocturnal periods associated with feelings of tension and depression is demonstrated. There was no significant alteration of potassium excretion. (Table VII.)

CASE I. The patient was a forty-four year old semi-skilled laborer with rheumatic heart disease. There was evidence of aortic stenosis, mitral insufficiency, auricular fibrillation and a recent pulmonary embolus. He was in congestive heart failure on admission. Six weeks later when he was fully digitalized and diuresis was completed, he was transferred to the metabolic ward where he was maintained on a 1,000 mg. sodium intake. Early in the course of the observations, the patient's pulse rate was consistently noted to be between 88 and 94 per minute. Since he was still fibrillating, and in order to slow the rate further, the dosage of digitalis was increased. The patient was obviously depressed and withdrawn for the next forty-

TABLE V

TOTAL SODIUM EXCRETION IN MEQ. DURING TWELVE-HOUR NOCTURNAL PERIODS IN COMPENSATED CARDIAC PATIENTS ON CONSTANT WATER AND ELECTROLYTE REGIMEN

Case No.	Tranquil $\bar{x}$	Range	No. of Observations	Tense or Depressed $\bar{y}$	Range	No. of Observations	$D = \bar{y} - \bar{x}$
I	19.7	12.6–23.6	10	12.8	3.4–15.7	9	−6.9
II	41.6	30.3–47.6	6	19.8	15.5–25.0	3	−21.8
III	29.5	25.0–34.0	10	21.6	17.0–24.1	7	−7.9
IV	15.9	8.4–30.5	14	8.6	5.9–14.4	4	−7.3
VIII	45.3	34.8–65.5	3	20.7	12.4–35.6	3	−24.6
For five subjects: $\bar{D} \pm SD_D = 13.7 \pm \sqrt{76.3}$					$t = 3.51$	$p < 0.02$	
V	43.0	28.7–62.5	13	...	...	0	...
VI	17.6	4.6–32.3	10	7.7	...	1	−9.9
VII	46.6	18.4–70.1	18	...	...	0	...
For eight subjects: $\bar{D} \pm SD_D = 13.1 \pm \sqrt{22.5}$					$t = 2.76$	$p < 0.05$	

TABLE VI

TOTAL URINARY VOLUME IN CC. DURING TWELVE-HOUR NOCTURNAL PERIODS IN COMPENSATED CARDIAC PATIENTS ON CONSTANT WATER AND ELECTROLYTE REGIMEN

Case No.	Tranquil $\bar{x}$	Range	No. of Observations	Tense or Depressed $\bar{y}$	Range	No. of Observations	$D = \bar{y} - \bar{x}$
I	780	525–960	10	617	290–865	9	−163
II	1627	1250–2000	6	1618	1605–1625	3	−9
III	1509	1285–1695	10	1223	1145–1525	7	−186
IV	1017	490–1365	14	699	440–925	4	−318
VIII	989	683–1170	3	653	275–936	3	−336
For five subjects: $\bar{D} \pm SD_D = 202 \pm \sqrt{17,609}$					$t = 3.41$	$p < 0.02$	
V	1453	1070–1885	13	...	...	0	...
VI	1276	970–1510	10	1100	...	1	−176
VII	783	545–1245	18	...	...	0	...
For eight subjects: $\bar{D} \pm SD_D = 198 \pm \sqrt{4795}$					$t = 7.00$	$p < 0.01$	

eight hours; however, it was not until the third day that the cause of his depression was realized. His wife called on that day and stated "my husband and I both know he is worse because you had to increase his heart medicine." After completion of the study, both sodium and water excretion were found to be markedly decreased during this period despite the increase in the dosage of digitalis. Ordinarily one would expect digitalis therapy to increase the output of sodium [*6*].

Near the end of the study a chest pain developed similar to that experienced with a pulmonary embolus prior to his admission although on this occasion there was no clinical or radiologic evidence of embolus. However, the patient was very depressed. He feared that chest pain such as this would prevent his return to work. In the thirty-six-hour period following the chest pain his sodium excretion was 37 per cent and water output was 62 per cent of that observed during tranquil periods.

Near the termination of the study the patient was

TABLE VII

TOTAL POTASSIUM EXCRETION IN MEQ. DURING TWELVE-HOUR NOCTURNAL PERIODS IN COMPENSATED CARDIAC PATIENTS ON CONSTANT WATER AND ELECTROLYTE REGIMEN

Case No.	Tranquil $\bar{x}$	Range	No. of Observations	Tense or Depressed $\bar{y}$	Range	No. of Observations	$D = \bar{y} - \bar{x}$
I	11.8	9.7–14.4	10	12.8	4.7–16.9	9	+1.0
II	31.9	24.5–38.5	6	29.6	28.5–31.3	3	−2.3
III	27.7	22.5–31.0	10	31.2	26.8–41.0	7	+3.5
IV	27.3	14.5–39.9	14	22.5	15.3–36.5	4	−4.8
VIII	22.6	17.1–27.9	3	24.3	15.8–33.6	3	+1.7
For five subjects: $\bar{D} \pm SD_D = 0.18 \pm \sqrt{3.01}$					$t = 2.32$	$p > 0.05$	
V	32.7	16.7–49.4	13	...	...	0	...
VI	32.4	20.4–48.3	10	23.1	...	1	−9.3
VII	25.1	14.1–40.5	18	...	...	0	...
For eight subjects: $\bar{D} \pm SD_D = 1.7 \pm \sqrt{16.3}$					$t = 1.03$	$p > 0.10$	

given a moderate salt load consisting of a three-fold increase in daily sodium intake. During two tranquil periods of twelve hours each, sodium output averaged 40 mEq. The following day the patient was informed he was ready for discharge but that he would not be able to return to work. The Veterans Administration could not offer him any financial assistance. He became discouraged and during the subsequent two periods (each twelve hours in length) of depression, sodium output was reduced to 24 mEq. despite a sodium intake of 140 mEq.

CASE II. This patient was a forty-five year old white man with hypertension who was admitted in severe cardiac failure. He was digitalized and given a 1,000 mg. sodium diet. Mercuhydrin® and ammonium chloride were successfully used for diuresis. After compensation and stabilization of weight, urine collections were started. This patient had no financial resources to care for his wife and two children during his illness. One day his wife informed him there was no food at home and no money, and he became very depressed. That day the twelve-hour sodium output was only 6.1 mEq., compared with an average output of 30.5 mEq. on tranquil days. The following day he continued to be withdrawn and depressed, and his sodium output remained low at 12 mEq. Following a discussion of his financial and occupational difficulties, during which no reassurance was given, his twelve-hour sodium output was 4.5 mEq. with urine volume reduced to 695 cc. from an average during tranquil periods of 1,471 cc.

CASE III. This patient was a sixty-three year old white man with arteriosclerotic heart disease and a syphilitic aortic aneurysm. He was admitted in moderate decompensation. After stabilization of weight he was maintained on a 1,000 mg. sodium intake. He had been a Sunday school teacher at the time he contracted syphilis and had never told his wife about it. After he was informed of the relationship between syphilis and his aneurysm, his sodium output decreased to 40 per cent (13 mEq.) of that observed during tranquil periods (29 mEq.). He seemed tense and controlled during the long hours his wife spent at his bedside. Again, during the twelve hours following a discussion of his extramarital acquisition of syphilis and its potential effect on his wife and his position at church, the patient felt depressed at their potential rejection of him and sodium output was decreased to 5 mEq. Upon termination of the study the patient's wife decided to cancel plans to take him home. The patient who was aware of his wife's decision gained two pounds during the subsequent forty-eight-hour period in contrast to a previously stable weight and despite his standardized fluid regimen.

CASE IV. This patient was a fifty year old white man who had recently retired from full time service in the Army. He had emphysema and evidence of right heart failure. He was also thought to have arteriosclerotic heart disease. He was maintained on a 1,000 mg. sodium diet and his weight was stabilized following satisfactory diuretic therapy. He was considered to be depressed or tense during only eight of a total of forty-six observation periods (each twelve hours in length). During each of these eight periods there was a significant reduction in urinary volume and sodium output and a small decrease in potassium excretion, as shown in Tables II through VII. More

marked urinary changes were observed in this patient during the short term experimental periods (10 to 11 A.M.). He had difficulty lying quietly without falling asleep. On one occasion when he slept during an entire hour of daytime recumbency the output was 165 cc. water with a sodium excretion of 1.1 mEq. For the next 10 to 11 A.M. period he was informed that he must remain awake while recumbent and was not to read or listen to the radio. During this hour the patient successfully stayed awake but the effort made him tense. Urine output was decreased to 30 cc. with a sodium content of 0.13 mEq. During a recumbent hour in which he was depressed by a discussion of the possibility of leaving his friends to enter an old soldiers' home, urine output was again reduced to 30 cc. with a sodium content of 0.26 mEq.

CASE V. This patient was a forty-eight year old white man with arteriosclerotic heart disease who had previously had two myocardial infarctions. He was admitted in congestive failure. After compensation he was maintained on a 2,000 mg. sodium intake. During two interviews (each one hour in length) in which he discussed his unsatisfactory marriage and other difficulties which engendered in him a feeling of "hopelessness," sodium output was markedly decreased, averaging 2.1 mEq. per hour compared with an average of 5.6 mEq. per hour during two control periods with the patient in the supine position but not depressed. This patient liked to paint, was very meticulous in his work, and took great pride in it. During periods of concentration on his painting there was a marked reduction in the volume of urine and in the output of sodium, with no significant decrease in potassium output.

CASE VI. This patient was a man forty-three years old with hypertensive heart disease. His blood pressure remained fairly constant at a level of 210/130 mm. Hg. His renal function, however, remained good. His weight on admission to the hospital was 243 pounds, some 75 pounds above his dry weight. During his hospital stay of ten weeks on the metabolic ward, all twenty-four-hour weight gains of 1½ pounds or more correlated clearly with events which aroused feelings of tension or depression. On one occasion his father was hospitalized because of a stroke. He had no word about his father's condition for two days and thought his father was near death. He was depressed, and gained weight during this time. On another occasion, after a mistaken complaint that the nurses were not following the doctor's orders, he apologized to each nurse who came to his room, one time having tears in his eyes. During the forty-eight-hour period in which this experience occurred he gained more than four pounds in weight. Similar events could be found accompanying each of the major periods of weight gain. During the three weeks of metabolic study reported here, he consistently excreted less sodium in his urine than was ingested but gained only three pounds in weight.

This patient was easily disturbed by other patients and by minor changes on the ward; however, he slept well at night. It was interesting to note that his twelve-hour daytime sodium output averaged 3.8 mEq., while his twelve-hour nocturnal sodium output averaged 17.6 mEq. Since he remained recumbent through many of the daytime periods, body position would not seem an adequate explanation of these differences.

In this patient, as in others, there was a decrease in sodium excretion in association with feelings of depression. However, there was no decrease in volume as had been found in the other patients and as previously reported in tense or depressed healthy subjects [*4*]. This discrepancy, occurring in a patient who was in more severe decompensation on admission than were the other patients, will be discussed later.

CASE VII. This patient was a forty-two year old man with hypertensive cardiovascular disease who was admitted in marked failure. After compensation he was maintained on a 1,500 mg. sodium diet. He was a quiet, lonely, obese gentleman who had both financial and domestic difficulties. During four periods of observations (each 12 hours in length) which were characterized by depression, there was retention of sodium and volume, as seen in Tables II and III.

CASE VIII. This patient was a forty-five year old carpenter with arteriosclerotic heart disease and mild angina pectoris who was admitted in moderate congestive failure. During the early part of his hospitalization he lost fourteen pounds on the usual therapy. After weight was stabilized he was transferred to the metabolic ward and was continued on a 1,600 mg. sodium intake. Early one evening his chest pain returned, for the first time during his hospitalization, and he became markedly discouraged. During the next twenty-four-hour period his sodium output was decreased to 22 mEq. from a usual twenty-four-hour average of 84 mEq.

Reassurance and Relaxation Following Inhibitory States. During periods when reassurance and encouragement were given to these patients, e.g., when one patient (Case I) was reassured that his cardiac status was not deteriorating, diuresis of sodium and water was noted. Feelings of relaxation following episodes of depression were likewise accompanied by increased excretion of sodium and water. These data are summarized in Table VIII.

EXCITATORY STATES

Excitement, Apprehension and Anger. In Table IX urinary sodium excretion rates observed in

TABLE VIII

EXCRETION RATES ASSOCIATED WITH REASSURANCE AND RELAXATION FOLLOWING TENSION OR DEPRESSION (TWELVE-HOUR PERIODS)

Case No.	Time	H_2O (cc.)			Sodium (mEq.)			Potassium (mEq.)		
		Reassured	Tense	Difference	Reassured	Tense	Difference	Reassured	Tense	Difference
I	Day	745	557	188	23.3	12.7	10.6	14.4	27.4	+13.0
I	Day	640	557	83	38.4	12.7	25.7	23.8	27.4	+ 3.6
I	Night	870	617	153	39.2	12.8	26.4	11.9	12.8	+ 0.9
III	Day	1330	1001	329	28.0	11.0	17.0	29.0	35.0	+ 6.0
IV	Day	1470	743	727	21.5	7.3	14.2	37.4	26.4	−11.0
		$\bar{D} \pm SD_D = 296 \pm \sqrt{66083}$ $t = 2.57$ $p < 0.05$			$\bar{D} \pm SD_D = 18.8 \pm \sqrt{9.85}$ $t = 6.02$ $p < 0.01$			$\bar{D} \pm SD_D = 2.5 \pm \sqrt{77}$ $t = 0.64$ Not significant		

TABLE IX

SODIUM EXCRETION DURING THIRTY-FIVE PERIODS OF EXCITEMENT, APPREHENSION OR ANGER

Time	Case No.	Tranquil $\bar{x}$	Range	Number	Excitatory $\bar{y}$	Range	Number	$D = \bar{y} - \bar{x}$
Day	I	20.5	15.7–24.0	12	38.4	33.2–44.4	3	17.9
	III	29.0	14.0–55.0	7	31.0	...	1	2.0
	IV	14.6	9.0–21.5	18	22.8	...	1	8.2
	V	49.3	40.8–64.2	23	76.7	43.7–109.8	2	25.4
	VI	3.6	1.9– 7.5	8	5.7	3.9– 7.3	4	2.1
	VII	36.3	21.5–54.6	16	34.4	...	1	−1.9
	VIII	42.2	24.1–51.3	6	78.9	76.9–80.9	2	36.7
Night	I	19.7	12.6–23.6	10	39.2	35.2–41.4	3	19.5
	II	41.6	30.3–47.6	6	74.8	...	1	33.2
	III	29.5	25.0–34.0	10	28.7	23.0–34.5	2	−0.8
	IV	15.9	8.4–30.5	14	32.4	28.0–38.5	3	16.5
	V	43.0	28.7–62.5	13	51.8	27.0–70.0	8	8.8
	VI	17.6	4.6–32.3	10	21.6	13.1–24.9	4	4.0

$\bar{D} \pm SD_D = 13.2 \pm \sqrt{164.6}$
$t = 3.71$
$p < 0.01$

association with thirty-five periods of excitement, apprehension and anger as compared with excretion rates during periods of tranquility are recorded. During periods characterized by excitation there was a highly significant diuresis of sodium in comparison to periods of tranquility. No significant variation in volume or potassium excretion was noted.

CASE VIII. This patient was having prolonged and marked difficulty in evicting a family from an expensive home he owned in spite of having won several court decisions. One day during this study he looked out of his seventh floor window and thought he saw the family enter the hospital. At the sight of them, his anger flared anew. He ran down eight flights of stairs into the basement and up again but could not locate them. In spite of this tremendous activity, his sodium

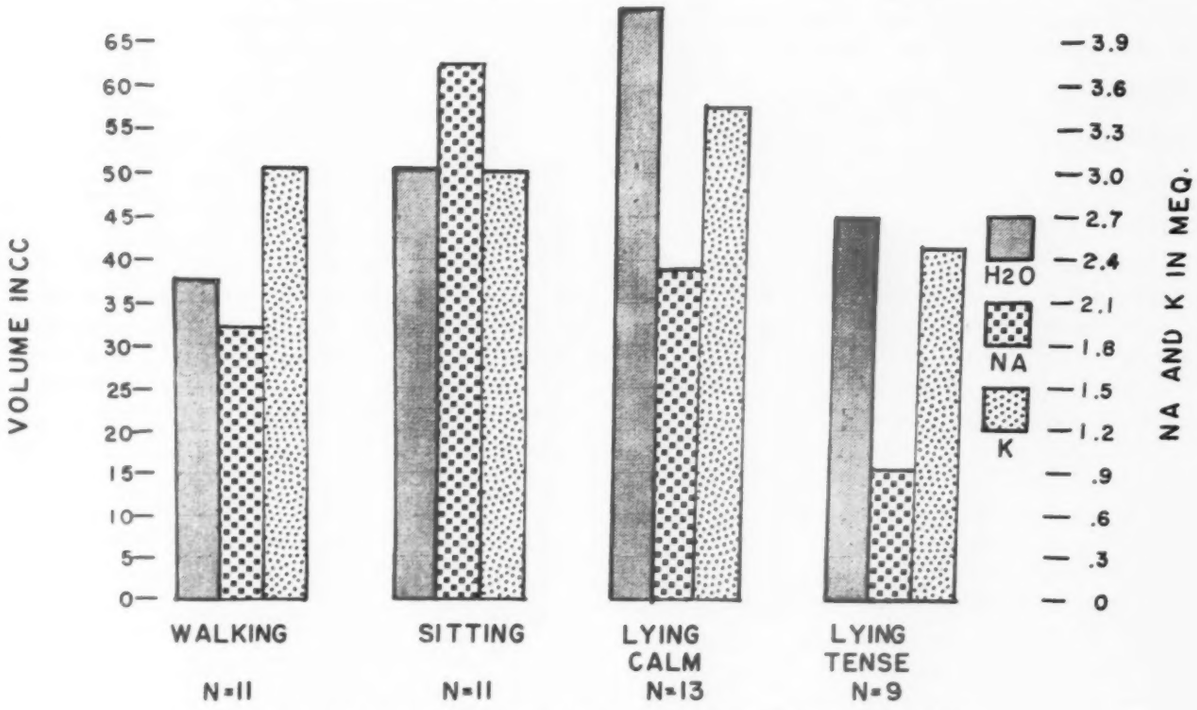


FIG. 2. Mood, position and renal excretion in four subjects for one hour periods.

output for that period was increased 60 per cent over tranquil periods spent sitting in bed! There was a 1¼ pound weight loss during this period. There was no sodium retention that night. The following day the patient was discouraged and expressed a hopeless feeling; both water and sodium output were decreased to 50 per cent of the output observed during the period of excitement. Sodium and volume outputs for this period were 848 cc. and 39.3 mEq. compared with values of 1,710 cc. and 77 mEq. for the twelve-hour period characterized by excitement.

CASE V. This patient was previously described as being hostile to his second wife. He often discussed the virtues of his first wife who had left him to marry another man. One day he saw his first wife and for the next forty-eight hours was in a state of excitement. His sodium output for these two days was increased by 40 per cent and water output was increased 60 per cent despite increased muscular activity. Potassium excretion was unaltered.

CASE IV. This patient had three nocturnal periods (each twelve hours in length) characterized by restless apprehension or anger. Urinary volume averaged 1,415 cc. during these periods compared to an average of 1,017 cc. during tranquil periods. Sodium output averaged 32.4 mEq. during the twelve-hour periods of apprehension or anger compared to an average of 15.9 mEq. for tranquil periods. Potassium excretion was unchanged.

Body Position and Physical Activities. The effects of changes in body position and muscular activity were studied in four of the subjects. On separate days the hour from 10 to 11 A.M. was spent walking, sitting or in the supine position. During some of the periods of recumbency, tension was induced by interviews or by requiring the performance of a task that required concentration.

The results shown in Figure 2 demonstrate a decrease in urinary volume and in sodium excretion with walking as compared to the output of these substances with the patient sitting or lying. Such changes have previously been reported by others. However, this response was greatly altered during emotionally charged events. If the patient were tense or depressed while in the supine position, decrease in both urinary volume and sodium output was observed.

Frequently these patients were more relaxed while sitting than while lying. One patient (Case 1) disliked lying in bed in the daytime. He was tense at such times and his sodium output was 0.9 mEq. per hour. He was more relaxed while sitting and his sodium output increased to 3.4 mEq. per hour in that position.

Alterations in excretory pattern related to the emotional state of the patient were sometimes

greater than were the changes in excretory pattern attributable to body position or muscular activity. In one patient (Case VI) the sodium output was thirty-two times greater during an hour of vigorous activity while he was unusually angry than it was during two periods of sitting while tense.

COMMENTS

Retention of sodium was noted during periods characterized by feelings of despair, hopelessness and depression and during periods of tension, but in these cardiac patients retention of water seemed less marked than that previously reported in healthy subjects during similar emotional states [*4*]. The patient who had suffered the most severe decompensation (Case VI) showed no significant alteration in urinary volume in association with feelings of depression, although there was significant sodium retention. A recent study suggests that there may be an increased release of antidiuretic hormone independent of osmoreceptor control in the patient with severe congestive heart failure [*7*]. The patient with severe failure would therefore have marked water retention and urinary volume would be less susceptible to variation. Additional investigation will be necessary to determine the importance of antidiuretic hormone to the observations reported here.

Another mechanism which might be a factor in producing these urinary alterations is aldosterone secretion, perhaps secondary to changes in arterial vessel size occurring in association with stress. At the present time there is insufficient experimental evidence to implicate aldosterone secretion as a mechanism for these urinary alterations. It is of interest, however, that in 1957 Luetscher and Lieberman [*8*] reported that fifteen female patients with "idiopathic" edema excreted excessive amounts of aldosterone in the urine. They described these patients as "conscientious persons, living and working under some strain, and having symptoms of tension and emotional lability." The edema was observed to fluctuate with environmental factors, fatigue and emotional reactions of the patient.

Although each patient consumed the same quantity of sodium each day, the urinary excretion of sodium varied greatly. These fluctuations correlated well with changes in emotional state. It is apparent that urinary sodium determinations do not reliably reflect the care with which a patient is following a regimen of rigid salt restriction. When urinary sodium is determined as a diagnostic procedure, the emotional state of the subject should be evaluated since values obtained during periods of emotional stress may be markedly different from those obtained during tranquil periods.

It is common to find that patients with heart failure have had some precipitating factor for the episode of decompensation. Excessive exercise, infection, and increased sodium intake have frequently been mentioned. To these should be added emotional stresses. During periods of tension or depression sodium output may be reduced to less than 20 per cent of the output during tranquil periods. This suggests that in the patient with decreased cardiac reserve, prolonged periods of tension or depression could lead to serious derangements of homeostasis by the mechanism of fluid and sodium retention. If the physician is alert to the presence of feelings of depression or tension in his cardiac patients, he can often relieve these feelings. Certainly he can avoid actions and statements which might enhance such feelings. While the physician is caring for the patient he should be aware of the therapeutic importance of his relationship. In the patient with congestive failure, reassurance and encouragement may be associated with a diuresis of water and sodium.

SUMMARY

Eight male patients with compensated congestive heart failure (and stabilized as to weight) were studied on a metabolic ward. Sodium and water intake was maintained constant. All urine was collected, the volume noted, and sodium and potassium excretion measured. These data were kept completely separate from a daily appraisal of the behavior, attitudes and emotional state of the subject. The contribution of the position of the body and muscular activity to the excretory pattern was also controlled and evaluated.

Wide fluctuations in renal excretion of fluid and electrolytes were observed in all patients; these fluctuations could be correlated with attitudes and emotions. In situations which evoked feelings of discouragement or tension, renal excretion of water and sodium was decreased. The decrease in volume was often not proportionate to the marked retention of sodium, perhaps due to an increase in antidiuretic hormone in advanced congestive failure.

In situations which evoked a reaction of excitement, anger or apprehension, renal excretion rates of sodium were increased as compared with excretion rates observed during neutral periods. A diuresis of sodium and water was also associated with periods of reassurance and active relaxation. Such alterations in excretory pattern related to the emotional state of the patient were sometimes greater than those attributable to body position or muscular activity.

There was no significant variation in potassium excretion which could be correlated with a specific emotional state.

The findings suggest that in the patient with decreased cardiac reserve prolonged states of tension or depression may be a precipitating factor for an episode of decompensation by the mechanism of fluid and sodium retention. A reassuring attitude on the part of the physician may be of substantial importance in the therapy of congestive heart failure.

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Effect of Shock and of Vasopressor Drugs on the Regional Circulation of the Brain, Heart, Kidney and Liver*

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With the recent widespread use of vasopressor drugs in the treatment of shock, controversial evidence regarding their efficacy is accumulating. It has been suggested that these agents may have a deleterious effect upon certain organs and may even cause necrosis in the liver and kidney [*1,2*]. If this is true, the free use of these drugs in shock must be seriously questioned.

In order better to understand the rationale of vasopressor therapy, the effect of shock and of vasopressor drugs on blood flow to vital organs was investigated in the experimental animal. Although regional blood flow to these organs has been studied extensively in the past, there is still some disagreement regarding the effect of shock and of vasopressor agents on these organs. This is particularly true of the splanchnic region.

In the past, most determinations of blood flow through the liver and kidney have utilized the Fick principle, bromsulphalein excretion being used for the liver [*3–8*] and clearance usually of paraaminohippuric acid for the kidney [*9–11*]. These indirect methods of blood flow determination depend upon the functional integrity of the parenchymal cells of the organs studied and are therefore subject to large errors in shock states in which ischemia may severely disturb cellular function [*11*]. A different technic for these measurements was clearly desirable. The regional flow in shock was therefore reinvestigated, using a flowmeter that allowed continuous flow measurements of many organs at the same time. Using the photoelectric dropmeter, it was possible to measure blood flow directly and continuously in the hepatic artery, portal vein, renal vein, coronary artery and carotid artery. Such direct continuous measurements of blood flow, made in several organs simultaneously, minimized the large error in flow measurement and gave a more complete picture of what happens to blood flow through these organs during all phases of acute shock and vasopressor therapy. Observations were made only during the acute phase of shock. No attempts were made to study the hemodynamics of prolonged, irreversible shock.

METHOD

In forty-six dogs, anesthetized with pentobarbital, the chest and pericardial sac were opened and the anterior descending coronary artery was freed from its adjoining veins. The artery was severed and catheters were inserted proximally and distally. The abdomen was opened, the renal vein, portal vein and hepatic artery were severed, and catheters were immediately inserted proximally and distally. The other end of these catheters was inserted into the photoelectric dropmeter so that the flow in each organ was re-established and measured continuously with an intact peripheral resistance. A dropmeter was also inserted into the common carotid artery. Because the internal carotid artery of the dog is too short for cannulation, the proximal and distal catheters were inserted into one common carotid artery and all branches of the external carotid artery on that side were ligated so that the flow measurements would indicate the blood flowing solely into the internal carotid artery. The animals were heparinized prior to cannulation. The accuracy of the photoelectric dropmeter [*12–15*], which was first described by Clementz and Ryberg [*12*], has been improved upon by recording each individual drop and then determining blood flow by reference to predetermined calibration curves [*78*]. With these simple flowmeters, blood flow through the anterior descending coronary, one internal carotid artery, the hepatic artery, portal

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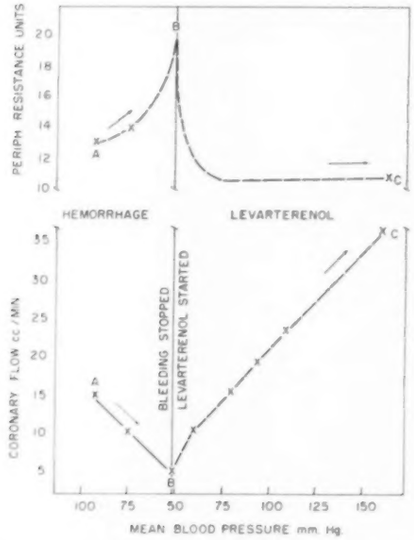


FIG. 1. *Lower portion*, the effect of reducing the mean systemic blood pressure from 100 to 45 mm. Hg and then restoring it by administering levarterenol. The coronary flow increases when levarterenol is administered. *Upper portion*, the change in peripheral resistance of coronary artery flow. Levarterenol therapy decreased the peripheral resistance of the coronary circulation.

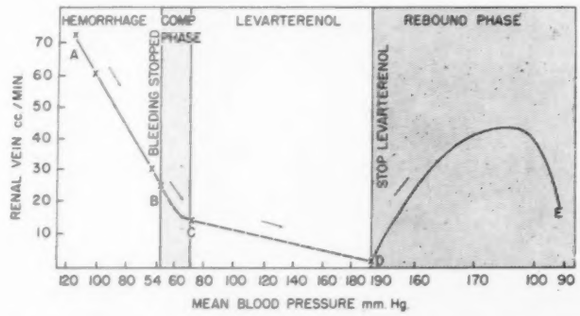


FIG. 2. The effect on renal vein blood flow of lowering the systemic blood pressure by bleeding the animal (A to B). When blood pressure dropped from 120 to 50 mm. Hg, renal vein flow diminished from 73 to 25 cc. per minute. The hemorrhage was stopped and the blood pressure spontaneously increased from 50 to 72 mm. Hg (B to C). During this "period of compensation," the renal blood flow decreased from 25 to 14 cc. per minute. Levarterenol was administered (C to D) and the renal flow decreased further from 14 to 1 cc. per minute. When the administration of levarterenol was discontinued, blood pressure dropped from 190 to 75 mm. Hg. During this "rebound" period (D to E), renal blood flow increased temporarily.

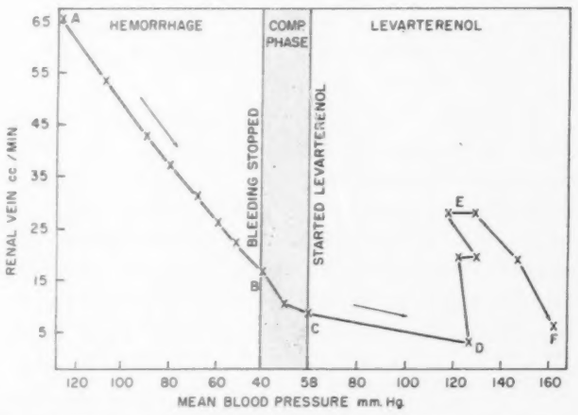


FIG. 3. The effect upon the renal vein blood flow of lowering the blood pressure by bleeding (dog). When the blood pressure was reduced from 125 to 40 mm. Hg (A to B), the renal blood flow diminished from 64 to 17 cc. per minute. Immediately after the hemorrhage was stopped, the blood pressure spontaneously rose to 58 mm. Hg (B to C). During this "period of compensation," the renal vein flow diminished from 17 to 10 ccs. per minute. Levarterenol was administered (C) and renal flow diminished further (D). However, after the levarterenol drip was slowed the renal vein flow increased somewhat (E). When the levarterenol drip was increased again, renal vein flow diminished (F).

vein and renal vein was continuously recorded simultaneously with systemic blood pressure using an electronic multichannel recorder. If not already in shock due to the surgical procedure, the animal was bled until blood pressure fell to a level of 45 mm. Hg. The effects of restoring blood pressure by giving (1) blood transfusion, (2) levarterenol and (3) metaraminol were then studied.

RESULTS

The Coronary Artery Flow. When systemic blood pressure was reduced by bleeding the animal, coronary flow diminished in the anticipated linear fashion and the coronary resistance increased. (Fig. 1.) When blood pressure was restored by blood transfusion, the coronary flow increased to its control measurements and the peripheral coronary resistance returned to normal. When blood pressure was raised by the administration of levarterenol coronary flow increased above the control value and the peripheral coronary resistance diminished markedly.

The Renal Blood Flow. When systemic blood pressure was reduced renal blood flow diminished accordingly and renal vascular resistance increased markedly. (Figs. 2 and 3.) When systemic blood pressure was restored by transfusion renal flow and resistance returned to control levels. (Fig. 4.) When blood pressure was restored by the administration of levarterenol, renal flow decreased further and resistance increased markedly. (Fig. 2, C to D; Fig. 3, C to D.) However, when the blood pressure was maintained at a constant normotensive level by slowing the levarterenol drip, renal blood flow increased after a period of time and renal vascular resistance decreased somewhat, al-

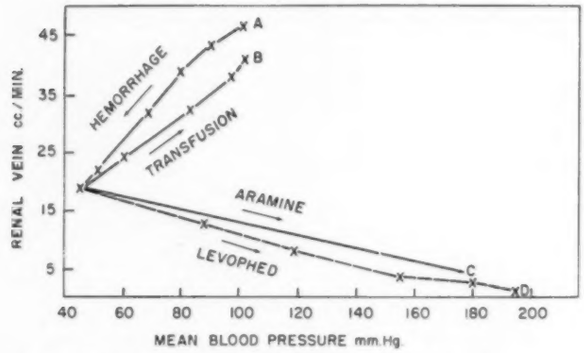


FIG. 4. The effect of lowering the mean blood pressure in the dog (A) and then restoring the blood pressure by administering metaraminol (C), levarterenol (D) and blood transfusion (B). Note that metaraminol and levarterenol caused almost the same degree of decrease in renal vein flow.

though it did not return to its control level. (Fig. 3, D to E.) When administration of the vasopressor drugs was discontinued, there was a sudden rebound upsurge in renal blood flow and drop in renal vascular resistance concomitant with a sudden drop in systemic blood pressure. (Fig. 2, D to E.) Results of metaraminol administration were similar to those obtained for levarterenol. (Fig. 4.)

Although renal blood flow is diminished when vasopressor drugs are administered, urine flow continues because of reduced tubular reabsorption. The urine has a fixed, low specific gravity.

Hepatic Blood Flow. Approximately two-thirds of the hepatic blood flow is obtained from the portal vein under normal conditions, the remaining one-third is supplied by the hepatic

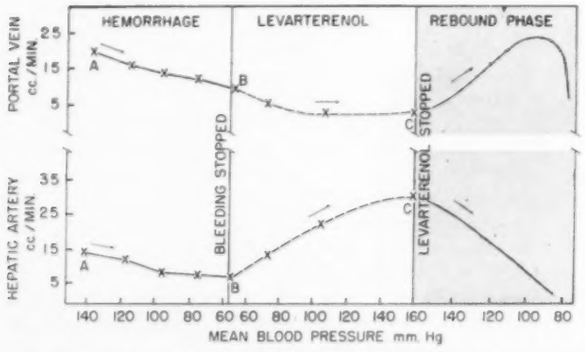


FIG. 6. The effect upon the portal vein and the hepatic artery flows of lowering blood pressure by bleeding (dog) (A to B). When levarterenol was administered, portal vein flow diminished further; however, hepatic artery flow increased considerably (B to C). When levarterenol therapy was discontinued blood pressure fell but portal vein flow increased temporarily (C to D).

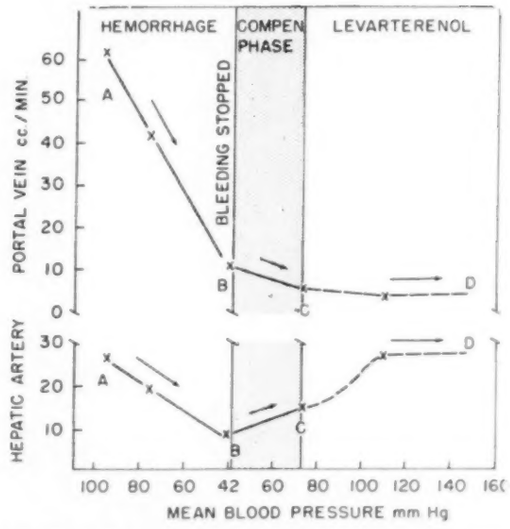


FIG. 5. The effect of the blood pressure on simultaneously recorded portal vein and hepatic artery blood flows. When blood pressure was reduced by bleeding (dog), portal vein and hepatic artery flows both diminished (A to B). Immediately after the bleeding was stopped the systemic blood pressure spontaneously rose from 43 to 74 mm. Hg. During this "compensatory phase" (B to C), portal vein flow decreased further but hepatic artery flow increased. When levarterenol was administered portal vein flow diminished further but hepatic artery flow increased (C to D).

artery [*16*]. When systemic blood pressure was lowered both the hepatic artery and the portal vein flows were diminished and their vascular resistances increased. (Fig. 6.) When blood pressure was restored by blood transfusion the portal vein and hepatic artery flows returned towards control levels. When blood pressure was restored to control levels by the administration of levarterenol or metaraminol the hepatic artery flow increased to its control values whereas, at the same time, the portal vein flow decreased further. (Figs. 5 and 6.) When blood pressure was maintained at normotensive levels for a period of time by regulating the levarterenol drip, the portal vein flow sometimes increased slightly. When blood pressure was raised to hypertensive levels by administering levarterenol in excess, the vascular resistance of the hepatic artery first decreased but later increased, with a resulting decrease in flow. Blood flow in the portal vein, however, diminished almost to zero when vasopressor drugs were used in excess to produce hypertension. This was undoubtedly due to an increase in mesenteric vascular resistance. When administration of the vasopressor drugs was discon-

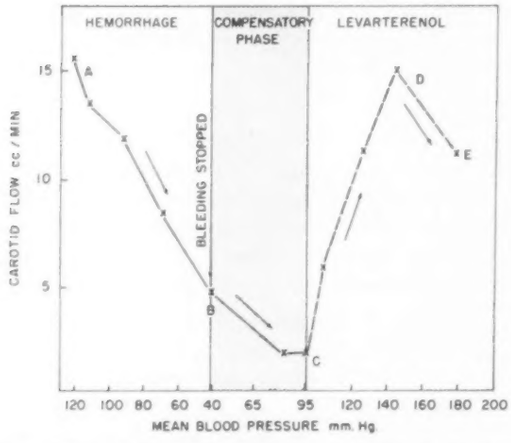


FIG. 7. The effect upon the internal carotid artery of lowering the blood pressure by bleeding the animal. When blood pressure was lowered (A to B), the carotid artery flow diminished. However, immediately after the bleeding was stopped the blood pressure rose spontaneously (B to C) and in this "period of compensation" carotid artery flow diminished further. When levarterenol was administered carotid artery flow increased (C to D); but when blood pressure was raised to hypertensive levels (D to E) carotid flow diminished again.

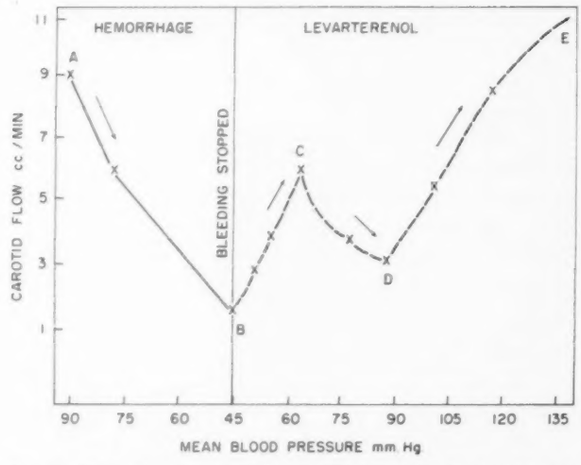


FIG. 8. The effect on carotid artery flow of reducing blood pressure by bleeding (dog). When levarterenol was administered carotid artery flow increased; however, when blood pressure was raised above 65 mm. Hg carotid artery flow diminished temporarily.

tinued there was a sudden rebound increase in portal vein flow for a short period of time as the blood pressure dropped. (Fig. 6.) This is similar to the rebound noted in renal blood flow. The changes in portal vein flow were similar to and occurred simultaneously with the changes in renal flow.

The total hepatic blood flow (portal vein and hepatic artery) was diminished when levarterenol or metaraminol was administered. The portal vein flow decreased more than the hepatic artery flow increased. The blood supply to the liver during treatment with vasopressor drugs is therefore principally arterial in origin. In this respect results of levarterenol and metaraminol administration were similar.

Internal Carotid Artery Flow. When systemic blood pressure was lowered the internal carotid artery flow diminished and there was a marked increase in peripheral carotid resistance. (Fig. 7.) When blood pressure was restored by levarterenol or metaraminol administration the carotid artery flow again increased and resistance diminished. If the systemic blood pressure was raised to hypertensive levels the carotid artery flow did not continue to rise but leveled off, or actually decreased, due to an increase in carotid artery resistance. (Fig. 7.) When the procedure was repeated, however, the responses were variable, indicating instability of the cerebral circulation. This phenomenon has been observed by others [*17*].

CLINICAL APPLICATION

The general belief that each organ has a characteristic vascular response to shock and vasopressor drugs is supported by these studies. A marked decrease in blood flow and increase in the peripheral resistance of the coronary, renal, hepatic artery, portal and cerebral circulations was observed during shock. (Figs. 1–8.) This decrease in flow and increase in vascular resistance is disproportionately large in the renal and splanchnic circulations. In shock, the compensatory mechanism involves redistribution of the remaining circulating blood volume apparently in an attempt to maintain adequate nutrition of the brain and heart. (Fig. 9.) This is accomplished by marked vasoconstriction of the musculocutaneous, renal and splanchnic circulations. (Figs. 2, 3, 5 and 8.) Penner and Bernheim [*18*] concluded from autopsy observations that ischemia of the intestine and kidneys occurred as a compensatory mechanism during shock. The concept of the preferential treatment of the brain and heart in shock was postulated by Sheehan [*19*] and by Franklin [*21*] although they had no experimental evidence in support of this view.

While this compensatory mechanism is usually effective in sustaining immediate life, it may result in ischemic damage to the organs in which severe vasoconstriction has occurred, hence the

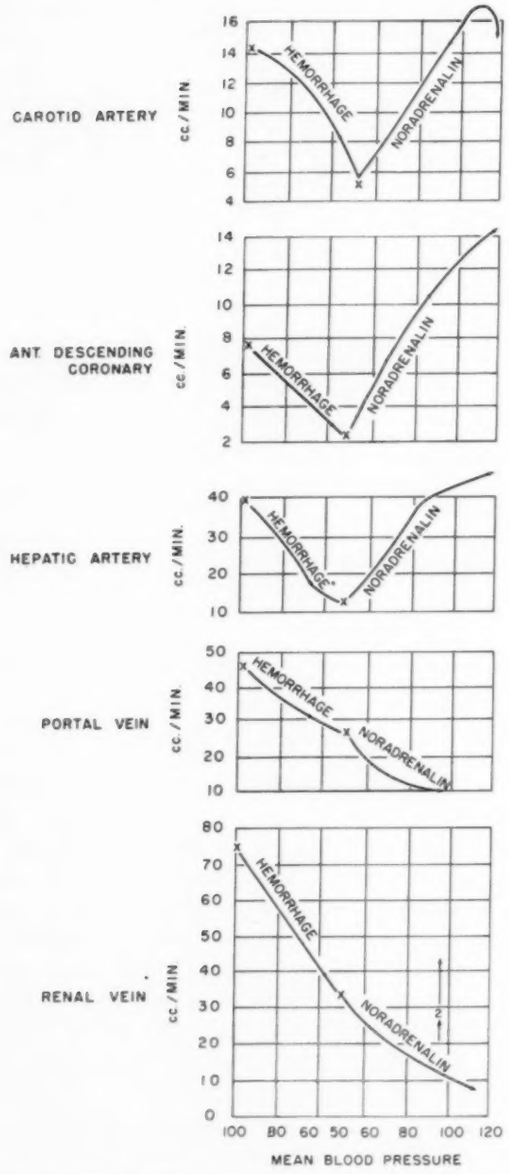


FIG. 9. A composite illustration which demonstrates the effect on the internal carotid artery, anterior descending coronary artery, hepatic artery, portal vein and renal vein of lowering the systemic blood pressure by bleeding (dog). The blood flow of each of these vital organs diminished when blood pressure was reduced by bleeding the animal. When blood pressure was restored by the administration levarterenol blood flow of the carotid, coronary and hepatic arteries increased but that of the portal and renal veins diminished. When blood pressure was raised to hypertensive levels carotid artery flow diminished again. Coronary artery flow increased considerably, due to vasodilatation.

occurrence of gangrene of the extremities [*22–26*] and necrosis of the liver [*27–31*], kidney [*18,19,20,32–39,151*] and intestine [*40–44*]. Since the brain and myocardium are even more sensitive to ischemia, cerebral [*45,46*] and myocardial [*47–50*] infarction often result from marked hypotensive states when the compensatory mechanism fails.

It has been shown experimentally by Field and Laverty [*51*] that the circulatory changes in acute shock are for the most part due to the release into the blood stream of humoral pressor substances. They concluded that neurogenic mechanisms in the circulatory adjustment to acute shock are overshadowed by the effect of the humoral factor, which is probably released by the sympathetic nerve endings. Manger et al. [*52*] have noted a marked elevation in the level of circulating catecholamines in the blood following hemorrhage. The use of vasopressor drugs in shock therefore seems merely to augment a normal physiological response to shock.

Some recent reports have suggested that the kidney [*1*], liver [*2*] and musculocutaneous system [*53*] may be damaged by vasopressor therapy. However, since damage to these organs is known to occur from shock itself, the evidence that pressor therapy *per se* has a deleterious effect on these organs is equivocal [*54*].

In sharp contrast to the vasopressor treatment of shock, some investigators have recommended the use of sympathetic blocking agents to counteract the intense vasoconstriction which occurs in shock, and hence improve the regional blood flow to these vital organs [*55–59*]. There has not, as yet, been sufficient clinical confirmation of the value of this sympathetic blocking concept and results to date have not been encouraging [*60*]. While sympathetic blocking agents might improve renal and intestinal blood flow, the resulting hypotension produced by administration of these drugs may prove lethal because of ischemia of the brain and heart.

CORONARY CIRCULATION

A reduction in systemic blood pressure is accompanied by a reduction in coronary blood flow [*61–69*], as indicated in this study. In addition, it has been noted that coronary artery resistance increases progressively as blood pressure falls. (Fig. 1.) Upon restoring the blood pressure with blood transfusion, the coronary flow and resistance returned to normal; coronary vasodilatation after the transfusion, as observed by Opdyke [*64*], did not occur. Upon raising the blood pressure by administering vasopressor

drugs there was a marked decrease in coronary resistance and increase in coronary flow (Fig. 1), as noted by many others [*70–78*]. The coronary flow increased linearly as the pressure was raised.

The retrograde coronary free flow, which represents the collateral blood flow [*79*], returned to control levels when blood pressure was restored by the administration of vasopressor drugs, but no evidence of vasodilatation of the collateral channels was observed. This is in sharp contrast to the marked vasodilatation that occurred in the peripheral coronary bed following administration of vasopressor drugs. It is believed that the collateral coronary circulation is derived from interarterial anastomoses and that it bypasses the peripheral coronary bed [*80*]. This belief is confirmed by the fact that the retrograde collateral blood flow is arterial in nature [*79–81*] and that vasopressor drugs are incapable of producing vasodilatation of the collateral vessels [*78*].

In the heart, the coronary arterial-venous oxygen difference under normal conditions is maximal, higher than in any other organ of the body. When the myocardium requires more oxygen, it obtains it not by increasing the oxygen extraction from the blood, since this is already almost maximal, but rather by increasing the coronary blood flow [*83*]. This is in contrast to other organs which are able to increase the oxygen extraction from the blood before an increase in blood flow through the organ is necessary.

Since decreased coronary flow associated with shock states, regardless of cause, may result in myocardial necrosis [*47–50*], heart failure due to weakness of the myocardial contraction [*82*], arrhythmias due to increased cardiac irritability, and conduction disturbances [*84,85*], coronary flow obviously must be maintained to prevent progression to irreversible damage. The true incidence of an arrhythmia "mechanism death" is difficult to ascertain because its detection requires constant electrocardiographic monitoring. Severe hypotension and reduced coronary flow may be induced by cardiac arrhythmias and this further aggravates the shock state [*84,85*]. By merely raising the blood pressure it was often possible to terminate various arrhythmias [*84–86*]. When vasopressor therapy failed to restore regular rhythm, the systemic and coronary blood pressures and coronary circulation were successfully maintained with pressor agents until antiarrhythmic drugs had time to become effective.

CEREBRAL CIRCULATION

The considerable differences of opinion expressed in the literature regarding cerebral hemodynamics [*87*] are partly due to differences in technic employed and partly reflect the variation in response of different species of test animals and the variable results obtained in the same animal. In the lower animals, the pial vessels have musculature and innervation and may respond to vasomotor stimuli. There is increasing evidence that in the higher animals vasomotor activity of the smaller cerebral vessels, such as the pial vessels, is lacking [*87*]; however, the larger arteries, as in the circle of Willis, may be able to contract [*88*].

In our studies, using the dog, cerebral vascular resistance increased as the blood pressure was lowered. When blood pressure was restored by blood transfusion cerebral artery flow and resistance returned to control levels. Immediately following the cessation of hemorrhage it was noted that systemic blood pressure rose slightly while, occasionally, cerebral flow diminished somewhat. (Figs. 7, B to C.) This same phenomenom occurred more frequently and was much more pronounced in the renal and portal vein flows following hemorrhage; this is discussed herein.

The administration of vasopressor drugs often restored cerebral blood flow when systemic blood pressure was raised to control levels. However, when the pressure was raised to hypertensive levels the cerebral blood flow "plateaued" or sometimes decreased, due to an increase in cerebral vascular resistance (Fig. 7), as observed by Moyer [*17*] in man. This could be a protective mechanism which prevents rupture of the cerebral vessels or the development of cerebral edema. Vasopressor drugs therefore are effective in increasing cerebral blood flow in shock only if blood pressure is maintained at normotensive levels. The decrease in cerebral blood flow and increase in cerebral vascular resistance observed when vasopressor drugs were given at hypertensive levels has been reported by other investigators using various technics [*89–92*].

In the young patient with an uncompromised cerebral circulation, hypotension may result in mental changes such as agitation, apprehension, psychosis, syncope or unconsciousness.

However, in the older patient with narrowing or occlusion of a cerebral artery, hypotension will cause failure of the collateral circulation and focal or generalized neurological changes or mental disturbances. The term "cerebral vascular insufficiency" has been applied to this condition [*93–95*]. If blood pressure is promptly restored focal neurological changes, such as hemiplegia, will disappear. Systemic hypotension due to reflex vasodepressor phenomena, hemorrhage, coronary occlusion, cardiac arrhythmias, anaphylaxis, hyperinsulinism, pulmonary embolism, hypersensitive carotid sinus, orthostatic hypotension or any other cause may result in transient cerebral disturbances. We and others [*93–96*] have demonstrated that the neurological changes of cerebral vascular insufficiency may be reversed by the use of vasopressor drugs, provided that effective treatment is administered early enough.

RENAL CIRCULATION

The estimated blood flow to the kidneys under normal conditions is 20 to 25 per cent of the total cardiac output [*11*]. Because of its copious blood supply and its well known labile vasomotor activity, the kidneys play an important role in the homeostasis of the circulatory system.

When blood pressure was lowered by hemorrhage the flow in the renal vein decreased and the vascular resistance of the kidney increased markedly. (Fig. 2.) When blood pressure was restored to normal levels by blood transfusion the renal vein flow and the renal vascular resistance returned to nearly normal levels. Marked impairment in renal blood flow during shock has been observed previously by many investigators using clearance technics [*11,98–101*]. Immediately after the cessation of hemorrhage the systemic pressure rose slightly while, at the same time, the renal blood flow continued to decrease. (Fig. 2, B to C; Fig. 3, B to C.) This further decrease in renal blood flow in the presence of a concomitant increase in systemic blood pressure was also observed by Selkurt [*11*] and represents a compensatory vasoconstriction in the kidney which is part of the homeostatic mechanism during shock, as noted by Lauson et al. [*99*].

When vasopressor drugs were used to restore the blood pressure in traumatic or hemorrhagic shock renal blood flow decreased further and, at the same time, renal vascular resistance increased. (Fig. 2, C to D.) This further decrease in renal blood flow was observed to occur during the rise in blood pressure. However, if the administration of levarterenol was so regulated that the blood pressure could be maintained at a constant normotensive level for a period of time, the renal blood flow often increased slightly. (Fig. 3, D to E.) Using clearance studies, Moyer et al. reported that when vasopressor drugs were administered to hypotensive subjects [*97,102,105*] an increase in renal blood flow to almost normal levels occurred. More recently Marson [*104*], who made direct blood flow measurements of the renal vein in shock, reported that the administration of levarterenol resulted in a further decrease in renal blood flow. This is in sharp contrast to the earlier reports by Moyer. We always observed a further decrease in renal blood flow in shock immediately following the administration of levarterenol; however, after a period of time, a slight increase in renal blood flow was often seen. By the time this increase in renal blood flow occurred a considerable volume of intravenous fluid had usually been infused with the levarterenol and this increase in circulating blood volume may explain the improved renal blood flow. The most consistently effective way of improving renal blood flow in shock was to reinfuse the animal with some of the withdrawn blood.

If blood pressure was raised to hypertensive levels with larger doses of levarterenol renal blood flow was always severely impaired and often "shut down" or ceased completely at pressure levels above 200 mg. Hg systolic. This decrease in renal blood flow with the use of vasopressor drugs with the pressure at hypertensive levels has been reported by Moyer [*102,105*] and others [*101,106–109*].

When administration of the drug was discontinued and the blood pressure decreased there was a marked rebound increase in the renal blood flow. (Fig. 2, D to E.) This sudden upsurge in renal blood flow accompanying a drop in blood pressure following cessation of levarterenol administration is in keeping with the occurrence of ganglionic blockade which Duner and von Euler [*103*] have shown to be present for several hours following the administration of levarterenol. This is responsible for a marked fall in blood pressure to levels below those before administration and sometimes poses a clinical problem when administration of levarterenol is discontinued.

It was found that the administration of

metaraminol and levarterenol had almost identical effects on renal circulation during shock. This is contrary to previous observations [*97*] utilizing clearance studies in shock, which indicated that metaraminol therapy caused less impairment of renal blood flow than did levarterenol, and that the former drug therefore was superior [*97*].

It is commonly observed that when small doses of epinephrine or levarterenol are administered the excretion of urine increases, whereas when large doses of these drugs are given the urine volume is decreased [*110*]. It is believed that with small doses of levarterenol or epinephrine vasoconstriction of the efferent arterioles occurs, resulting in an increase in glomerular filtration rate. With large doses of these drugs vasoconstriction of both afferent and efferent arterioles occurs, resulting in marked diminution of renal blood flow and decrease in glomerular filtration rate; this occurs when the drugs are used to produce hypertensive levels of blood pressure.

It has long been known that shock states cause disturbances in renal function of varying degrees of severity, manifested by proteinuria, oliguria, anuria, electrolyte imbalance, azotemia and other abnormalities. Depending on the etiology of shock and severity of the renal damage, this disturbance in renal function may be classified as crush syndrome [*33–35*], lower nephron nephrosis [*33,38,39*], acute renal failure [*37*], acute anuria [*37*], shock kidney and the like [*36*]. Both functional and histologic evidence indicate that the organic damage is in the tubule. These tubular lesions have been found in shock states due to surgery [*39,150*], myocardial infarction [*111*], ventricular tachycardia [*38*], trauma [*34–37,100*], cardiac failure [*151*], dehydration due to vomiting, dysentery [*149*], diabetic coma and in obstetrical shock [*19,20*]. It is now widely accepted that this renal damage is due to ischemia resulting from vasospasm of the renal vascular bed, in addition to the fall in systemic blood pressure.

Transient proteinuria is often observed in normal persons under stressful conditions such as fright, severe exercise and cold. These stimuli cause an increase in the urinary excretion of catecholamines [*112*]. Orthostasis is also associated with an increased urinary excretion of catecholamines [*113*]. King and Baldwin [*114*] have discussed proteinuria under these conditions and conclude that the production of renal ischemia by the release of catecholamines into the blood stream is the common mechanism. Renal ischemia has been shown to be capable of producing proteinuria by Starr [*115*] and Chesley [*116*]. Evidence that the catecholamines can produce renal injury in man is supported by the occurrence of renal damage in patients with pheochromocytoma [*117*]. It was shown long ago that repeated injections of epinephrine will produce bilateral renal cortical necrosis in normotensive animals [*18*]. It would be difficult, however, to be certain that levarterenol itself will produce renal necrosis in shock, as suggested by Boughton [*1*], since shock alone will produce the same changes.

HEPATIC CIRCULATION

Total hepatic blood flow is generally considered to contribute approximately 40 per cent of the venous return to the heart under normal conditions [*118*]. Knowledge of the behavior of the hepatic circulation in shock is incomplete and conflicting because of the complexity of the interrelationship of the circulation derived from its two components, the hepatic artery, and the portal vein. The latter is directly affected by the mesenteric circulation. In studying the blood flow of the liver, therefore, the vasomotor activity of the mesenteric circulation must also be considered; we have found that this is quite different in its responses from the hepatic artery.

Previous investigations of hepatic blood flow have largely utilized the bromsulphalein dye excretion technic [*3–8*]. The amount of bromsulphalein excreted by the liver is determined not only by the hepatic blood flow but also by the functional status of the parenchymal liver cells. Disturbances of cell function, such as occur in shock, may therefore materially affect the flow determinations. Another method of determining total hepatic blood flow is by use of the thermostromuhr, which measures the thermal conductivity in the liver [*119–123*]; this method is based on the principle that the thermal conductivity is linearly related to the amount of blood flow. A few investigators have measured portal vein or mesenteric blood flow directly, using either the rotameter [*124*] or the bristle flowmeter [*125*]. More recently, a method of measuring mesenteric blood flow indirectly, by the use of radioactive isotopes, has been reported [*126*]. In the present study direct blood flow measurements in the portal vein and hepatic artery were made continuously and simultaneously.

As blood pressure was reduced by hemorrhage, blood flow in both the hepatic artery and the portal vein decreased (Figs. 5 and 6), in conformity with the decreased total hepatic blood flow in shock observed by others using both dye excretion [*127–130*] and thermal conductivity [*131*] methods of measurement. Immediately after the cessation of hemorrhage the blood pressure rose slightly while, at the same time, the portal vein flow decreased further. (Fig. 5, B to C.) This marked vasoconstriction of the portal or mesenteric circulation occurred simultaneously with that in the renal vein. Previous measurements of portal vein flow in acute shock recorded a decrease in flow but did not indicate a significant increase in mesenteric vascular resistance [*124,125,133*]. It is thus apparent that the mesenteric circulation also plays a vital role in circulatory homeostasis, along with the kidney. This confirms the postulate of Franklin [*21*] and of Sheehan [*19*] that, in shock, vasoconstriction of the renal and splanchnic circulation occurs with preferential treatment of the brain and heart.

The misconception that the abdominal viscera are wholly spared from circulatory embarrassment in shock is no longer tenable. There is presently an increasing awareness of the occurrence of ischemic damage during severe shock in the organs supplied by the mesenteric circulation. Ende [*44*] reported several cases of intestinal necrosis in patients dying of severe congestive heart failure and shock who at postmortem had no demonstrable mesenteric vascular occlusion, i.e., thrombus or embolus. It was his conclusion that the intestinal necrosis was a result of vasospasm. Gastrointestinal mucosal ulcerations (stress ulcers) and hemorrhage are a common finding at postmortem following severe shock, probably, as Penner and Bernheim [*40,41*] pointed out, a result of ischemia secondary to vasospasm. Pseudomembranous enterocolitis may, in some instances, be a complication of shock and not of antibiotic therapy *per se*; this might explain why pseudomembranous enterocolitis was described before the advent of antibiotic therapy. It must be concluded, therefore, that necrosis of the intestine may occur in shock just as it does in the kidney. The experimental facts now confirm the clinical evidence.

The resistance in the hepatic and mesenteric arteries increased with hemorrhagic shock and returned to normal when blood pressure was restored by transfusion. When blood pressure was raised to normal levels by the administration of levarterenol or metaraminol portal vein flow decreased further and, at the same time, hepatic artery flow increased towards normal levels. (Figs. 5 and 6.) At hypertensive levels the hepatic artery flow rate reached a plateau or decreased slightly due to an increase in hepatic artery resistance while, at the same time, the portal vein flow decreased further and occasionally ceased altogether, due to a marked increase in mesenteric vascular resistance. (Fig. 5.) However, if blood pressure was sustained at near normal levels by regulating the levarterenol intravenous drip, portal vein flow increased slightly. This increase occurred simultaneously with the increase in renal vein flow but was usually of less magnitude. How much of this slight increase in blood flow might be due to the volume of intravenous fluids administered is a matter of speculation. After cessation of the levarterenol administration, and as the blood pressure fell, there was a sudden rebound rise in portal vein flow, simultaneously with and similar to that observed in the renal vein. (Fig. 6, D to E.)

Sympathetic stimulation has long been suspected of producing mesenteric vasoconstriction [*134–140*]. Recently Deal and Green [*141*], using an electromagnetic flowmeter, have shown that stimulation of the splanchnic nerve and injection of epinephrine and norepinephrine all produce vasoconstriction of the mesenteric vascular bed. Levy has reported mesenteric vasoconstriction when levarterenol was administered during acute shock [*133*]. His portal flow measurements bypassed the liver and therefore vasoconstriction of the portal bed in the liver as the cause of decreased portal blood flow can be eliminated.

As previously mentioned, the bromsulphalein excretion technic [*142*] and the thermostromuhr [*143*] reveal that vasopressor drugs produce a slight decrease in total hepatic blood flow. From our flow curves it is apparent that when pressor agents are administered portal vein flow diminishes while hepatic artery flow increases. The resultant decrease in portal vein flow is not sufficiently compensated for by the increase in hepatic artery flow, resulting in a slight net decrease in total hepatic blood flow which is now principally arterial in nature.

Brunson et al. [*1*] have stated that the incidence of liver necrosis has increased in the years since vasopressor drugs have been used. How-

ever, central necrosis of the liver is known to occur in shock alone. Because 70 per cent of the oxygen supply of the liver under normal conditions is supplied by the hepatic artery [*16*], and also because hepatic artery flow after the administration of levarterenol is usually almost equal to the control flow, it is doubtful that levarterenol administration will cause necrosis of the liver, unless arteriovenous shunts are opened up.

The possibility that vasopressor drugs may aggravate the ischemia of the intestine already produced by the shock state must be considered. Cone [*144*] recently reported the occurrence of intestinal necrosis in a young child with a pheochromocytoma who died in a hypertensive crisis. Penner and Bernheim [*145*] have produced ulcerations of the digestive tract of dogs by the repeated injections of epinephrine. It is therefore reasonable to assume that an overdosage of levarterenol may produce ischemic lesions of the intestine. Patients in whom a mesenteric infarction is suspected clinically should not be given vasopressor drugs because of the danger of producing more mesenteric ischemia and a more extensive infarct.

Ischemic damage of the intestine due to vasospasm can result from severe shock, excessive vasopressor drug administration, reflex vasospasm due to mechanical obstruction of a large vessel or any combination of these. The term "mesenteric vascular insufficiency" may serve to describe any situation in which the mesenteric blood flow is insufficient to supply the nutritional demands of the tissues which it perfuses. Its manifestations are protean, depending partly upon the severity and rapidity of the development of the vascular insufficiency [*146*].

SUMMARY AND CONCLUSIONS

Because previous indirect methods of measuring blood flow in various regions of the body in shock states have not been entirely satisfactory, a new technic was devised, utilizing photoelectric dropmeters, which has made it possible to measure blood flow in the cerebral, coronary, renal and hepatic circulation of dogs continuously and simultaneously.

The chief results of these studies indicate that (1) Each organ has its own characteristic vascular response to shock and vasopressor drugs. (2) The circulation of the intestine as well as that of the kidney plays a vital role in circulatory homeostasis during acute shock. The vascular resistance in each of these organs increases markedly following hemorrhage. (3) The use of vasopressor drugs in shock increases the circulation to the brain and the heart while, at the same time, the blood flow to the intestine and kidney is diminished.

Several conclusions of clinical significance may be drawn from these experimental findings. (1) Pressor drugs may be lifesaving because they restore the circulation of the brain and the heart. These organs cannot sustain ischemic states as well as the kidney and the intestine. (2) When thrombosis of the coronary or cerebral vessels has occurred, the tissue is nourished by the collateral circulation. This collateral circulation will fail unless blood pressure is maintained. Therefore, following a coronary or cerebral artery occlusion, measures should be taken to maintain blood pressure or correct an attendant hypotension. (3) The risk of producing intestinal and renal damage must be considered insignificant when weighed against the risk of myocardial or cerebral infarction.

The concept of "mesenteric vascular insufficiency" is discussed and may explain some acute and chronic disturbances of intestinal function which are at present poorly understood.

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Combined Aortic and Mitral Stenosis*

A Clinical and Physiological Study

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ALTHOUGH much information concerning acquired lesions of a single heart valve has been reported, relatively little attention has been given to the pathophysiology of multivalvular heart disease. Clinical analyses of combined stenosis of the aortic and mitral valves have usually lacked anatomical confirmation. Furthermore, when clinical and anatomical features have been correlated at operation or autopsy, the degree of stenosis often has been only grossly estimated.

This report presents an analysis of the clinical and physiological characteristics of a group of patients with combined aortic and mitral stenosis of known severity.

MATERIAL AND METHODS

Of 149 consecutive patients with acquired valvular heart disease studied by catheterization of the left side of the heart from 1955 to 1958, twenty-two patients shown to have combined mitral and aortic stenosis without severe regurgitation form the basis of this report. In eighteen patients the diagnosis was supported by the findings at operation upon one or both valves, or at autopsy. The series is unavoidably selected since many patients were referred for evaluation for surgical treatment, usually with progressive symptoms on medical therapy.

For purposes of comparison, similar analyses were made of seventeen patients with proved significant solitary aortic stenosis (fourteen with severe stenosis and three with moderate stenosis) and of twenty-four patients with proved significant solitary mitral stenosis (sixteen with severe stenosis and eight with moderate stenosis). These were all the patients with pure univalvular stenosis studied during this period.

Each patient was carefully evaluated clinically by at least two of us, and had a standard 12-lead electrocardiogram, chest fluoroscopy and roentgenograms, and usually a phonocardiogram. The intensity of the murmurs was graded from I to VI as described by Levine and Harvey [*1*]. The criteria of Sokolow and Lyon [*2,3*] were used in analyzing the electrocardiogram. Radiologic chamber enlargement was graded on a 1- to 4-plus scale.

The patients with combined aortic and mitral stenosis were studied by the following procedure. Catheterization of the left side of the heart was performed by posterior transthoracic puncture of the left atrium [*4,5*] with the patient in the prone position, under local anesthesia and mild sedation with barbiturates. A blunt, thin-walled 16 gauge needle was used, the obturator carrying the cutting edge. A polyethylene catheter (internal diameter 0.76 mm.) was advanced into the left atrium and left ventricle. A second needle was usually introduced into the left atrium parallel to the first. A 17 or 18 gauge Cournand needle was inserted into a brachial artery in nineteen patients, a polyethylene catheter (internal diameter 1.14 mm.) was advanced into the ascending aorta according to the technic of Seldinger [*6*] in eleven patients, and both procedures were performed in seven patients. Pressures were measured simultaneously in the left atrium, left ventricle and aorta or brachial artery or both in all cases. Catheterization of the right side of the heart by the venous route preceded left heart catheterization in twelve patients. In two other patients catheterization of the right side of the heart was performed by direct transthoracic puncture. The needles and catheters were connected by rigid

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plastic tubing or lead tubing to strain-gauge pressure transducers (Statham P23D or P23G), and the pressures were recorded on a direct-writing oscillograph (Sanborn). Mean pressures were obtained by electrical damping. Mean pressure gradients across the aortic and mitral valves were measured by graphic integration. All pressure gradients referred to are mean gradients.

Cardiac output was determined by the indicator-dilution technic [*7*] in nineteen patients. Evans Blue dye (T-1824) was injected into the left atrium. Blood was collected from the brachial artery either by fractional sampling at constant intervals or continuously through a cuvette densitometer [*8*]. The output of the densitometer was recorded on the direct-writing oscillograph, and the curve was calibrated by the integrated sample technic [*9*]. The concentration of dye in plasma was measured in a spectrophotometer (Beckman DU). In two patients (Cases 1 and 20) the cardiac output was measured by the direct Fick method.

Pressure gradients and cardiac output determinations were obtained nearly simultaneously. Estimates of the aortic and mitral valve areas were obtained according to the formula of Gorlin and Gorlin [*10*] using an orifice coefficient "C" of 1 [*11*]. An aortic or mitral valve with an area of 1 sq. cm. or less was classified as severely stenosed, of 1.1 to 1.9 sq. cm. as moderately stenosed, and of 2 sq. cm. or larger as mildly stenosed.

Vascular resistances were calculated according to the formulas used by Ellis et al. [*12*].

Left ventricular work (W_{LV}) was calculated from the following formula and expressed as kg. M./min./sq. M.:

W_{LV} = cardiac index $\times$ 1.055 $\times$ 0.0136 $\times$ (mean left ventricular systolic pressure − mean left ventricular diastolic pressure), where cardiac index is expressed in L./min./sq. M., mean pressures are expressed in mm. Hg, 1.055 is the specific gravity of blood, and 0.0136 is the factor converting pressure from mm. Hg to M. H_2O.

The systolic ejection period was defined as the interval between the points of intersection of the left ventricular pressure curve with the arterial pressure curve. When the brachial artery pressure curve was used a delay of 0.06 second was assumed and corrected. Mean left ventricular systolic and diastolic pressures were measured by graphic integration.

The presence of mitral regurgitation was evaluated by analysis of the left atrial pressure contours [*13,14*] and indicator-dilution curves [*14,15*].

Patients with solitary stenosis were studied in the same manner.

In Case 8 and in one case of solitary aortic stenosis the indicator-dilution curves were unsatisfactory. In two cases of solitary mitral stenosis the left ventricular pressure tracings were distorted by artefacts during systole. This incompleteness of data accounts for the difference in the number of cases in some of the groups analyzed.

RESULTS

As estimated by left heart catheterization, sixteen patients had severe aortic stenosis, which was combined with severe mitral stenosis in six and moderate mitral stenosis in ten. Three patients had moderate aortic stenosis with severe mitral stenosis in one, moderate mitral stenosis in another and mild mitral stenosis in the third. Of three patients with mild aortic stenosis, one had severe stenosis and two had moderate mitral stenosis.

Moderate tricuspid stenosis was found in one patient at catheterization (Case 5) and in one at operation (Case 15). There was no evidence of tricuspid stenosis in thirteen other patients at catheterization or in three others at autopsy.

Clinical Data

The clinical features are presented in Table I. The clinical estimate of the severity of symptoms was based on the classification of the New York Heart Association. One patient was in class II; seventeen were in class III; and four in class IV. All patients in class IV had severe aortic stenosis.

Rheumatic Background. A history of rheumatic fever or chorea was obtained in sixteen patients. Nine patients had had a single attack of rheumatic fever; two had had a single attack of chorea; two had had recurrent episodes of rheumatic fever; and three had had separate bouts of chorea and rheumatic fever. A high frequency of recurrent attacks of the rheumatic process has been reported in patients with multivalvular lesions [*16,17*].

Sex and Age (Table II). The sex incidence resembled that of solitary mitral stenosis, being approximately 1 male to 2 females, in contrast to the 7:1 male-female ratio found in solitary aortic stenosis.

At the time of referral for evaluation, the patients with combined stenosis had a mean age of 45.2 years, similar to the group with solitary mitral stenosis (42.5 years), but were younger than those with aortic stenosis (50.4 years). These sex and age characteristics are comparable to those reported by others [*16,18,19*].

Symptoms. The mean age of patients at the onset of their symptoms was 39.6 years (Table II), similar to that in solitary mitral stenosis, whereas

TABLE

CLINICAL DATA IN COMBINED

Case No.*	Age (yr.) and Sex	N.Y.H.A. Class.†	Symptoms‡									Rhythm	Blood Pressure (mm. Hg) S/D
			Dyspnea	Orthopnea	Paroxysmal Nocturnal Dyspnea	Palpitation	Hemoptysis	Angina	Dizziness or Syncope	Sweating	Systemic Emboli		
1	46, F	IV	+++	+++	+++	0	0	0	0	0	+	AF	140/70
2	43, F	III	+++	0	+	0	+	+	0	+	0	AF	130/80
3	49, F	III	++	+	+	+	0	0	0	0	+	AF	160/80
4	58, M	IV	+++	+++	+++	+	0	0	+	0	+	AF	125/75
5	50, F	III	++	0	0	+	0	0	0	0	0	AF	140/100
6	42, M	III	+++	+	++	+	0	+	0	0	+	NSR	130/80
7	61, F	III	++	0	0	+	0	0	0	0	0	AF	130/80
8	44, F	IV	++	++	+	+	0	+	+	+	0	AF	100/80
9	43, F	IV	+++	+++	++	+	0	0	0	+	0	AF	112/70
10	47, M	III	++	0	0	+	+	0	0	+	0	NSR	110/48
11	45, M	III	++	0	++	+	0	0	+	+	0	NSR	130/75
12	44, M	III	++	+	0	+	+	0	0	0	0	AF	130/70
13	43, F	III	++	++	0	0	+	0	0	0	0	AF	130/70
14	42, F	III	+++	++	++	0	+	0	+	0	0	NSR	150/50
15	23, F	III	+	0	0	+	0	0	0	+	0	AF	130/80
16	54, F	III	+	0	0	+	+	0	0	0	+	AF	154/100
17	46, F	III	+	+	0	0	0	0	0	0	+	AF	170/80
18	46, M	III	++	+	+	0	0	+	0	0	0	AF	122/80
19	28, F	II	+	0	+	0	0	0	+	+	0	NSR	105/65
20	55, M	III	++	++	0	0	0	0	+	0	0	AF	130/80
21	46, M	III	++	0	0	+	0	+	+	+	0	NSR	140/76
22	42, F	III	+	0	+	+	+	0	0	0	0	NSR	132/72

NOTE: AF = atrial fibrillation.
NSR = normal sinus rhythm.
M_1 = mitral first sound.
A_2 = aortic second sound.
(O.S.) = opening snap on phonocardiogram only.
S/D = systolic/diastolic.

* Cases 1–6: severe aortic stenosis (AS) and severe mitral stenosis (MS); 7–16: severe AS and moderate MS; 17: moderate AS and severe MS; 18: moderate AS and moderate MS; 19: moderate AS and mild MS; 20–21 mild AS and moderate MS; 22: mild AS and severe MS.

† N.Y.H.A. Class. = New York Heart Association Classification.

‡ + indicates present, 0 indicates absent, except for dyspnea, orthopnea and paroxysmal nocturnal dyspnea where +, ++, +++ indicate mild, moderate and severe.

§ N indicates normal, 0 indicates absent, − indicates decreased, + indicates present except for M_1 where + indicates increased.

‖ 0 indicates absent, + to ++++ indicates mild, moderate, marked and massive, a indicates aortic and m indicates mitral.

the mean age was significantly later in solitary aortic stenosis ($p < 0.05$). Similar results have been reported [*16,20*].

The mean duration of symptoms (Table II) in the combined group was 5.4 years, comparable to the group with solitary mitral stenosis. In contrast, the patients with solitary aortic stenosis as a group had a shorter duration of symptoms ($p < 0.10$).

The most frequent symptoms were dyspnea, fatigue and palpitation. (Fig. 1.) Dyspnea was usually of moderate severity. Approximately half of the patients complained of chest pain, orthopnea and paroxysmal nocturnal dyspnea; one-third gave a history of edema, hemoptysis, excessive sweating or dizziness. Systemic emboli had occurred in about a quarter of the group. Only three patients had syncope. None had pulmonary emboli or subacute bacterial endocarditis. Notwithstanding the high incidence of chest pain, typical angina pectoris was present in only a quarter of the entire group. None of the patients showed electrocardiographic evidence of myocardial infarction.

Although patients with aortic stenosis and patients with mitral stenosis behaved similarly in some respects, characteristic symptom complexes were associated with each lesion. Symptoms common to both aortic and mitral stenosis were represented in patients with the combined lesion, namely, dyspnea, fatigue, orthopnea and paroxysmal nocturnal dyspnea. Moreover, certain features of mitral stenosis, such as palpitation, hemoptysis and systemic emboli, were prominent. However, some symptoms common in isolated aortic stenosis, namely, angina, dizziness or syncope, and sweating were much less common in the combined cases, as has

I

AORTIC AND MITRAL STENOSIS

Signs‖										X-Ray‖				
			Murmurs											
			Aortic		Mitral									
M_1	A_2	Opening Snap	Stenosis	Regurgitation	Stenosis	Regurgitation	Aortic Systolic Thrill	Right Ventricular Heave	Left Ventricular Thrust	Electrocardiogram	Left Atrium	Left Ventricle	Right Ventricle	Ascending Aorta Dilatation	Valve Calcium
N	0	0	IV	II	0	III	+	0	+	LBBB	++	+++	+	+	0
+	−	+	IV	0	II	0	+	0	+	LVH	++	+++	++	0	0
N	0	+	III	II	III	III	+	0	+	LVH	++	++	0	0	a,m
−	0	(+)	III	0	0	II	0	+	+	0	+	++++	++	0	a
N	0	0	III	0	0	0	+	0	0	LVH	+	++	++	0	0
N	−	0	II	II	III	II	0	0	+	0	++	0	++	0	a,m
+	0	(+)	III	II	0	II	0	+	+	0	+	++	+++	0	0
N	0	0	IV	II	II	0	+	0	0	LVH	++	++	+	+	m
N	0	0	IV	I	II	II	+	0	+	LVH	+++	++	++	+	a
+	0	0	IV	II	0	II	+	+	+	LVH	+	+++	+	0	a
+	0	0	III	I	I	II	+	0	0	0	+	++	0	+	a,m
+	0	0	II	0	II	III	0	0	0	LVH	++	++	+	+	a,m
+	−	0	IV	II	III	III	+	+	+	LVH RVH	++	+	++	0	a,m
N	0	0	IV	III	0	IV	+	0	0	0	++	++	+	0	m
+	−	0	III	II	III	II	+	+	+	0	++	+	0	0	a
N	−	+	III	II	III	II	+	+	0	0	++	+	+	0	0
+	−	+	II	I	0	II	+	+	+	LVH	++	+	+	0	0
+	−	+	II	0	I	III	+	+	+	LVH	+	+	+	+++	a,m
+	0	0	IV	II	II	II	+	0	0	LVH	+	+	+	0	0
+	N	+	II	I	II	0	0	0	+	0	++	+	+	0	a
+	−	0	III	III	0	III	+	0	+	LVH	+	+++	+	++	0
+	N	+	II	II	III	I	0	0	0	0	++	0	0	0	a

NOTE: LBBB = left bundle branch block. RVH = right ventricular hypertrophy.
LVH = left ventricular hypertrophy. a = aortic. m = mitral.

TABLE II

COMPARISON OF SEX INCIDENCE, AGE AT ONSET OF SYMPTOMS, AND DURATION OF SYMPTOMS IN MITRAL STENOSIS, COMBINED AORTIC AND MITRAL STENOSIS AND AORTIC STENOSIS

Condition	Cases (No.)	Sex Incidence			Age at Onset of Symptoms (yr.)		Duration of Symptoms (yr.)	
		Male (%)	Female (%)	Male:Female	Range	Mean	Range	Mean
Solitary mitral stenosis	24	29	71	1:2.4	13–51	37.3	0.6–12	5.2
Combined aortic and mitral stenosis	22	36	64	1:1.8	16–60	39.6	0.6–16	5.4
Solitary aortic stenosis	17	88	12	7:1	24–62	48.4	0.1–12	3.1

also been noted by others [*19,21*]. Thus, 19 per cent of the patients with severe or moderate mitral stenosis combined with severe aortic stenosis complained of angina, and only one patient had syncope, while in the group with severe solitary aortic stenosis 43 per cent gave a history of angina and 29 per cent of syncope. In the clinical series of McGinn and White [*19*], angina was five times as frequent and syncope twice as frequent in solitary aortic stenosis as in combined aortic and mitral stenosis.

Signs of Mitral Stenosis (Fig. 2). The classic auscultatory triad of mitral stenosis, consisting of the loud and snapping mitral first sound (M_1), the opening snap and the diastolic rumble, was often absent. An accentuated M_1 was present in 59 per cent and an opening snap in 41 per cent. Two additional patients (Cases 4 and 7) had an

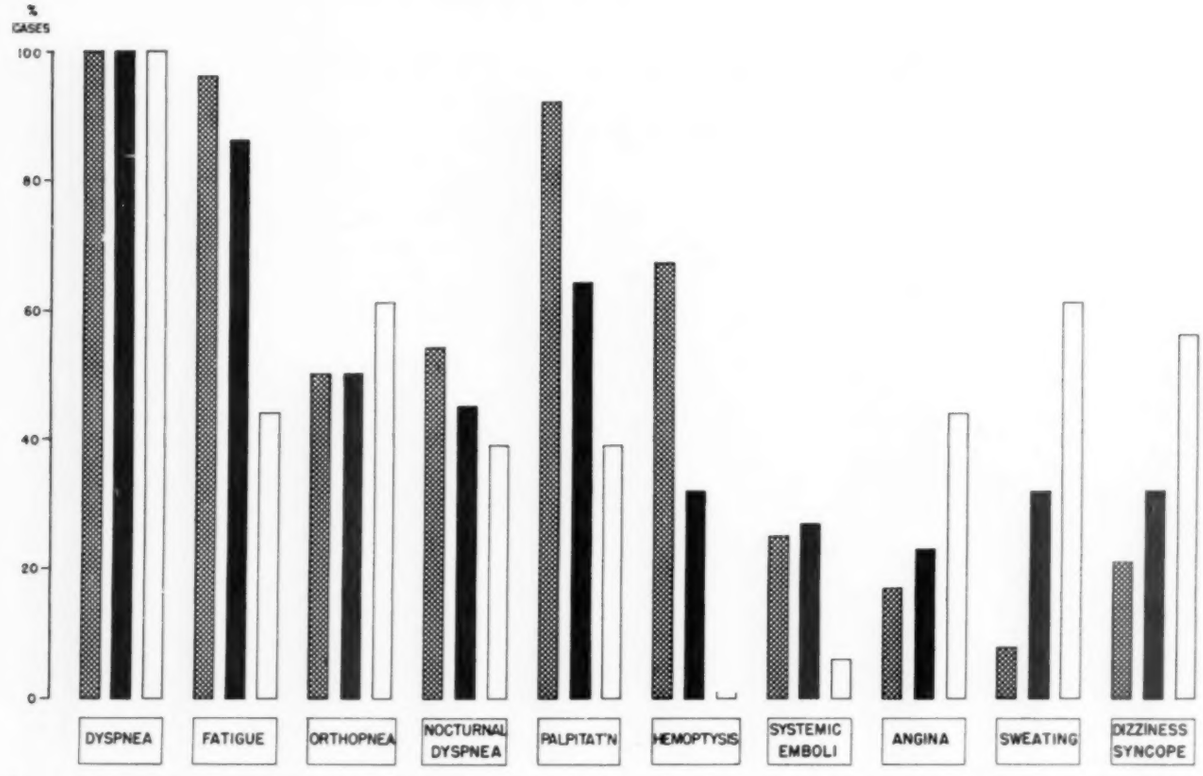


FIG. 1. Frequency of symptoms in solitary mitral stenosis (cross-hatched), combined aortic and mitral stenosis (solid black) and solitary aortic stenosis (white bars).

opening snap demonstrable only by phonocardiography. The diastolic rumble was present in only 68 per cent. Of the seven patients without a diastolic rumble, five had severe mitral stenosis and two had moderate mitral stenosis. Of these seven patients, one (Case 14) with normal sinus rhythm, a normal M_1, and no opening snap had a short apical mid-diastolic murmur which was not rumbling and had been interpreted as an Austin Flint murmur. In five of the seven patients the only apical diastolic murmur had all the characteristics of the murmur of aortic regurgitation. In the remaining case, diastole was completely clear at the apex.

The electrocardiogram showed atrial fibrillation in 68 per cent. Of the seven patients with normal sinus rhythm six had P-mitrale. In contrast, atrial fibrillation was present in only 6 per cent of the patients with solitary aortic stenosis, and although 44 per cent of those with normal sinus rhythm had abnormal P waves, none had classic P-mitrale.

In view of the frequency of a right ventricular heave by physical examination (36 per cent), and fluoroscopic findings of right ventricular enlargement (77 per cent), it was of interest that electrocardiographic evidence of right ventricular hypertrophy was present in only one patient. Four patients (Cases 4, 10, 17 and 18) with physical, radiologic and electrocardiographic findings of left ventricular enlargement had physical and radiologic findings of right ventricular enlargement, but their electrocardiograms gave no indication of right ventricular hypertrophy. Two of these patients were studied by right heart catheterization and had pulmonary hypertension. Thus, these cases illustrate the known masking effect of left ventricular hypertrophy on right ventricular hypertrophy [*22*], also evident in the control group with solitary aortic stenosis.

Fluoroscopic examination revealed enlargement of the left atrium in 100 per cent and calcification of the mitral valve in 45 per cent of the patients. On the other hand, approximately a half of those with solitary aortic stenosis had enlargement of the left atrium.

The physical signs of mitral stenosis were more frequently absent when the coexistent aortic stenosis was severe, as illustrated in Figure 2.

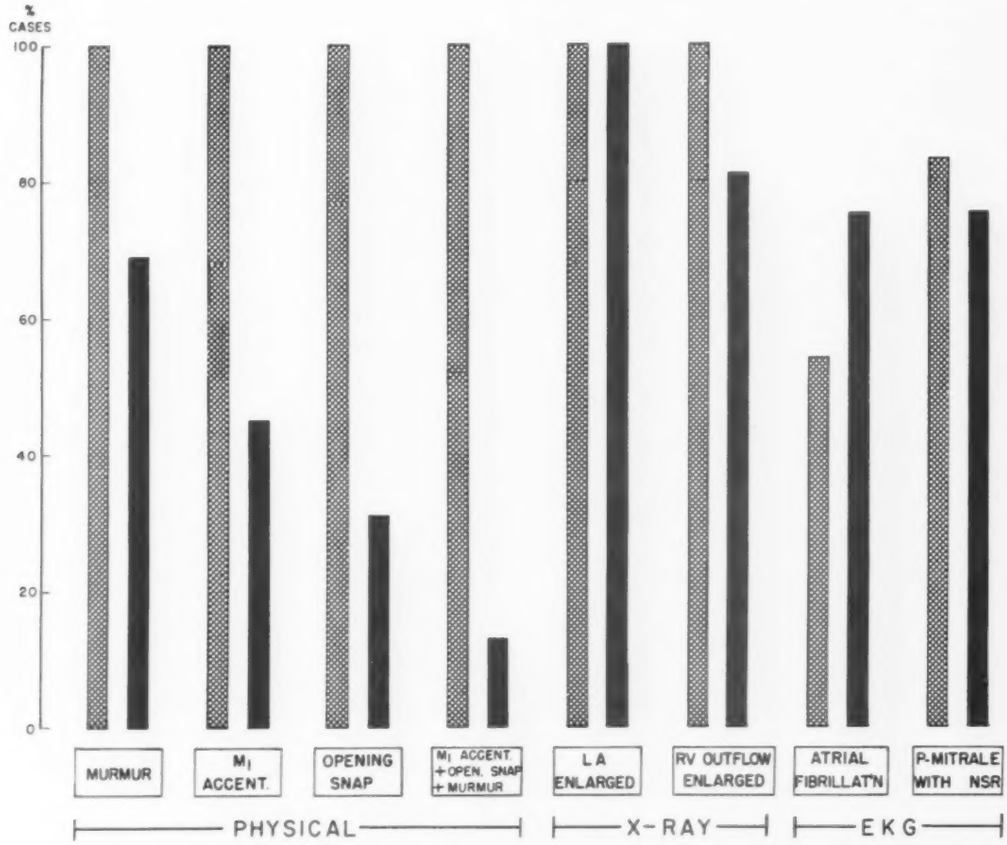


FIG. 2. Signs of mitral stenosis in solitary mitral stenosis (cross-hatched) and mitral stenosis combined with severe aortic stenosis (black bars).

The absence of the auscultatory findings of mitral stenosis is exemplified by the following patient with severe bivalvular stenosis:

CASE 1. A forty-six year old white housewife was admitted to the Boston City Hospital for the ninth time because of advanced heart failure. She was referred for cardiac evaluation. She gave a history of chorea at the age of eight years. She was subsequently asymptomatic except for dyspnea, orthopnea and edema of the ankles during each of five pregnancies between the ages of seventeen and thirty-three years. Dyspnea became more severe during the fourth pregnancy, and a heart murmur was described for the first time. Following her last pregnancy, during which time cardiac enlargement was found, dyspnea persisted, but usual activity was not limited.

Atrial fibrillation was first noted at the age of forty-two when she was hospitalized for biventricular heart failure. Therapy with low sodium diet, digitalis and diuretics was instituted. Three months later she suffered a cerebral embolism from which she completely recovered. The patient's activity became progressively restricted by dyspnea, fatigue and paroxysmal nocturnal dyspnea. Edema of the ankles occurred with increasing frequency, and intermittently there was gross congestive heart failure, including pleural effusion, necessitating hospitalization.

On examination the patient was dyspneic at rest, without cyanosis or clubbing. The blood pressure was 140/70 mm. Hg; the heart rate was 72 and irregular; the respiratory rate was 30. The neck veins were distended. At both lung bases there were inspiratory rales, and there was fluid at the right base. The heart was enlarged to the left anterior axillary line. A left ventricular thrust was present. There was no right ventricular heave. A_2 was absent, P_2 was moderately accentuated and M_1 was normal. There was no opening snap. A grade IV rough, diamond-shaped systolic murmur accompanied by a thrill was transmitted from the aortic area into the neck. A grade II blowing, decrescendo early diastolic murmur was transmitted from the aortic area to the apex. The liver edge was palpable 4 fingerbreadths below the right costal margin. Moderate edema of the ankles and pretibial areas was present. The peripheral pulses were normal.

The hematocrit was 47 per cent. The blood Hinton was negative. The electrocardiogram revealed a horizontal position, incomplete left bundle branch block and atrial fibrillation. Fluoroscopic examination showed cardiac enlargement with normal pulsations

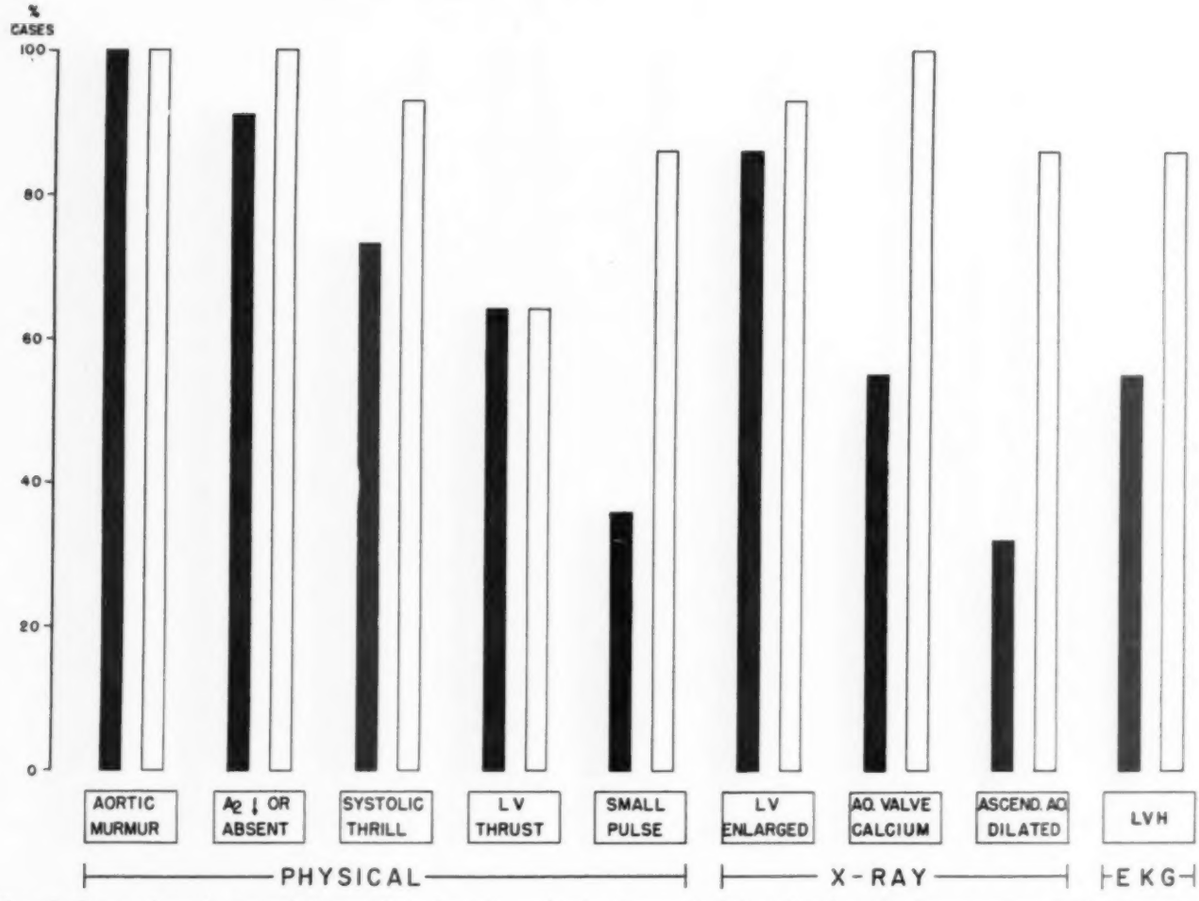


FIG. 3. Signs of aortic stenosis in combined aortic and mitral stenosis (black bars) and solitary severe aortic stenosis (white bars).

and without pulmonary vascular congestion. The left ventricle, left atrium and right ventricle were 3 plus, 2 plus and 1 plus enlarged, respectively. There was 1 plus dilatation of the ascending aorta. No intracardiac calcification was seen. The phonocardiogram also did not show an opening snap.

Signs of Aortic Stenosis (*Fig. 3*). All patients showed the typical systolic ejection murmur at the aortic area, usually accompanied by a thrill and transmitted into the carotid arteries. The murmur was loudest at the apex in two patients. There was no systematic relation between the loudness of the murmur and the severity of the aortic stenosis, although grade IV murmurs tended to be associated with severe aortic stenosis. A diminished or absent aortic second sound (A_2) occurred in all patients with severe or moderate aortic stenosis, but A_2 was normal in two patients with mild aortic stenosis.

A small, slowly ascending peripheral pulse was present in only eight patients, and a small pulse pressure was present in only one.

The apical thrust of left ventricular enlargement was present in 64 per cent of the cases and represented the only evidence for left ventricular enlargement in one patient. Left ventricular hypertrophy by electrocardiogram was present in only 55 per cent of the patients. One other had an incomplete left bundle branch block. Radiologic evidence of left ventricular enlargement was present more uniformly, occurring in 86 per cent. Only one patient with combined stenosis failed to show any evidence of left ventricular enlargement, and in this case the aortic stenosis was mild.

Calcification of the aortic valve and poststenotic dilatation of the ascending aorta occurred in 55 per cent and 32 per cent, respectively.

The frequency of signs of aortic stenosis in the entire combined group and in the subgroup with severe aortic stenosis was similar; thus these signs did not permit prediction of the severity of stenosis.

The absence of the radiologic and electrocardiographic signs of aortic stenosis is illustrated by the following case of severe aortic and mitral stenosis.

CASE 6. A forty-two year old white male laborer was admitted to the Boston City Hospital for the first time for cardiac evaluation. Swelling of the knees without other symptoms of rheumatic fever had occurred at age seventeen. He was subsequently asymptomatic until age twenty-seven when a cerebral embolism occurred, manifested by a transient right hemiplegia. At that time he was told of the presence of heart murmurs. He remained asymptomatic until eight months before admission, when progressive exertional dyspnea and palpitation developed. Concomitantly, angina pectoris, orthopnea and paroxysmal nocturnal dyspnea occurred. There was no history of hemoptysis, syncope, sweating or edema. Digitalis had been started six months before entry.

On examination the patient appeared comfortable and showed no cyanosis or clubbing. The blood pressure was 130/80 mm. Hg; the heart rate was 80 and regular; the respiratory rate was 20. The neck veins were not distended. The lungs were clear. The heart was slightly enlarged to percussion. There was no left ventricular thrust or right ventricular heave. The only thrill was at the apex in diastole. A_2 was diminished, P_2 was markedly accentuated and M_1 was normal. No opening snap was present. A grade II harsh, diamond-shaped systolic murmur was transmitted from the aortic area into the neck. A grade II blowing, decrescendo protodiastolic murmur was heard at the aortic area and along the left sternal border. A grade II blowing systolic murmur was transmitted from the apex to the left axilla. A grade III rough, low-pitched early and mid-diastolic murmur with presystolic accentuation was present at the apex. The liver and spleen were not enlarged. There was no dependent edema. The right and left dorsalis pedis and the right posterior tibial pulsations were absent, but the other peripheral pulses were unremarkable. There was a right facial weakness of the central type.

The hematocrit was 39 per cent. The blood Hinton was negative. The electrocardiogram was borderline normal without ventricular enlargement, showing a vertical position, normal sinus rhythm and P-mitrale. Fluoroscopic examination showed slight enlargement of the heart with normal pulsations and no pulmonary vascular congestion. The left ventricle was not enlarged. The left atrium and right ventricle were each 2 plus enlarged. There was no dilatation of the ascending aorta. There was calcification in the areas of the aortic and mitral valves. The phonocardiogram confirmed the auscultatory findings.

Regurgitation. Several patients had clinical features suggesting mitral regurgitation. Signs which raised this question included an apical systolic murmur of grade III intensity or louder, a normal first mitral sound, absence of an opening snap, systolic expansile pulsation of the left atrium and left ventricular enlargement. In combined stenosis these signs may not have the same significance as in pure mitral disease. Indeed, the physiological studies indicated significant regurgitation in only one patient (Case 13), and of the fifteen patients whose mitral valves were examined at operation or autopsy, regurgitation was judged mild in five (Cases 4, 12, 14, 15 and 21) and significant in none.

In seventeen patients an early diastolic murmur was heard along the left sternal border. However, none of the patients had other features of significant aortic regurgitation.

Systemic Blood Pressure. The blood pressure was normal except for three patients who had systolic pressures above 150 mm. Hg and one other who had an elevated diastolic pressure. The pulse pressure did not reflect the severity of the aortic stenosis. A pulse pressure of less than 40 mm. Hg was present in only one patient.

Hemodynamic Data

Data obtained at cardiac catheterization are presented in Table III. Estimates of valve size were in agreement with the anatomic findings in all patients observed at surgery or autopsy.

Cardiac Index (*Fig. 4*). The cardiac index of normal subjects measured with the indicator-dilution method in this laboratory is 3.60 L./min./sq. M., standard deviation 0.62 [*23*]. The cardiac index of patients with combined stenosis was significantly lower ($p < 0.05$). The cardiac index in this group was similar to that in solitary mitral stenosis but lower than in the group with solitary aortic stenosis, which approached the normal.

The mean cardiac index and stroke index were lower in the presence of atrial fibrillation (2.45 L./min./sq. M. and 28 cc./beat/sq. M., respectively) than with normal sinus rhythm (4.01 L./min./sq. M. and 46 cc./beat/sq. M., respectively).

Pressure Gradient and Flow Across the Aortic Valve (*Fig. 5*). The mean systolic pressure gradient across the aortic valve was 36 mm. Hg in the group with combined stenosis. When aortic stenosis was severe the mean gradient was 42 mm. Hg, standard deviation 17; it was below 30 mm. Hg in five patients and above 50 mm. Hg in only three. On the other hand, the gradient

TABLE III

HEMODYNAMIC DATA IN COMBINED AORTIC AND MITRAL STENOSIS

Case No.	Body Surface Area ($M.^2$)	Pressures (mm. Hg)							Flows				Total Pulmonary Resistance (dynes sec. $cm.^{-5}$)	Pulmonary Arteriolar Resistance (dynes sec. $cm.^{-5}$)	Total Left Ventricular Work (kg. M./min./$M.^2$)	Mean Pressure Gradient (mm. Hg)		Physiologic Valve Area (sq. cm.)		Anatomic Valve Area (sq. cm.)	
		Left Atrium (mean)	Left Ventricle (S/ED)	Arterial (S/D [mean])	Pulmonary Capillary (mean)	Right Atrium (mean)	Right Ventricle (S/ED)	Pulmonary Artery (S/D mean)	Cardiac Index (L./min./$M.^2$)	Stroke Index (cc./beat/$M.^2$)	Aortic Valve (cc./systolic sec.)	Mitral Valve (cc./diastolic sec.)				Aortic Valve	Mitral Valve	Aortic Valve	Mitral Valve	Aortic Valve	Mitral Valve
1	1.58	30	120/17	85/50(65)*	..	10	75/12	73/32(47)	2.03	22	159	114	1200	430	3.00	33	10	0.6	0.8	0.8	0.8
2	1.46	29	134/ 9	104/64(84)	20	3	70/ 3	65/35(47)	2.52	26	140	138	1112	639	4.28	29	20	0.6	0.7	0.5	0.7
3	1.67	19	163/ 9	103/45(68)	17	4	49/ 5	50/20(30)	1.89	30	157	79	659	286	3.29	35	9	0.5	0.6	0.5	0.7
4	1.68	17	135/13	100/50(72)	..	11	75/ 9	78/30(40)	2.11	32	202	144	877	329	3.36	25	9	0.9	0.9	0.6	0.9
5	1.51	14	118/10	68/38(53)*	13	8	31/ 7	30/ 8(18)	2.73	48	181	134	408	113	3.90	30	9	0.7	1.0	0.8	0.9
6	1.65	28	150/ 7	105/65(80)	..	11	53/ 8	52/29(34)	3.00	31	238	138	569	100	5.38	35	17	0.8	0.8	0.8	0.7
7	1.55	10	160/ 5	100/55(75)	..	..	...	...	1.68	17	90	124	...	...	3.51	53	6	0.3	1.1	0.4	1.1
8	1.55	20	130/ 8	100/80(90)	..	..	...	...	...	...	...	...	...	...	...	36	6	...	...	0.4	1.5
9	1.57	38	170/20	110/65(90)	..	..	...	...	2.85	29	138	177	...	...	5.53	45	16	0.5	1.1	...	...
10	1.58	26	220/ 8	135/60(88)*	..	..	...	...	3.60	45	258	196	...	...	9.54	84	18	0.5	1.2	0.5†	1.4†
11	1.79	28	187/ 8	127/74(101)	..	1	28/ 0	21/ 8(14)	4.29	43	344	278	165	52	11.07	69	21	0.9	1.3	0.6	...
12	1.80	27	153/ 6	110/90(103)	..	..	...	...	2.37	20	172	178	...	...	4.28	29	14	0.7	1.1	1.0	1.4
13	1.66	28	183/ 8	127/64(58)	..	5	40/ 5	...	2.92	31	215	175	...	...	5.58	46	26	0.7	1.2‡	0.7	...
14	1.49	18	174/ 7	100/50(80)	..	3	50/ 5	...	5.05	47	248	295	...	...	13.69	64	20	0.7	1.7	1.0	1.9
15	1.73	10	140/ 7	133/84(95)*	..	..	...	...	2.08	27	183	136	...	...	3.69	22	5	0.9	1.4	0.9	1.2
16	1.46	23	150/ 4	134/74(95)	..	..	...	...	2.95	22	226	173	...	...	5.68	32	13	1.0	1.2	...	...
17	1.49	24	187/13	185/93(123)	..	..	...	...	2.53	24	169	112	...	...	5.86	10	10	1.5	0.8	1.3	...
18	1.90	17	120/10	103/75(83)*	..	8	40/ 8	39/21(32)	2.77	29	273	223	487	198	4.53	31	8	1.1	1.8	...	...
19	1.38	10	120/ 8	85/55(73)	..	1	28/ 2	21/ 8(13)	5.22	69	351	260	144	33	7.49	32	5	1.3	2.5	...	...
20	1.70	11	105/10	95/65(80)	11	4	31/ 4	30/14(20)	2.90	30	270	158	320	160	3.71	10	5	2.0	1.5	...	1.5
21	1.73	13	118/ 5	110/66(75)*	14	2	35/ 2	30/13(18)	4.35	54	413	254	266	128	6.25	19	14	2.1	1.5	...	1.3
22	1.68	16	120/ 9	125/70(98)*	..	10	33/ 8	32/16(23)	2.53	36	287	145	395	132	3.81	8	10	2.3	1.0	...	1.0

NOTE: S = systolic
D = diastolic
ED = end diastolic

* Aortic pressure. All other arterial pressures obtained from brachial artery.

† Area determined at autopsy. All other anatomic valve areas were estimated at surgery.

‡ Physiological study indicated significant mitral regurgitation in this patient. Mitral valve area was corrected accordingly.

in solitary severe aortic stenosis (71 mm. Hg, standard deviation 21) was significantly higher ($p < 0.01$). Furthermore, patients with severe aortic stenosis and severe mitral stenosis had lower ($p < 0.05$) gradients (31 mm. Hg, standard deviation 3) than those with severe aortic stenosis and moderate mitral stenosis (48 mm. Hg, standard deviation 20). Similar relationships in solitary aortic stenosis and combined aortic and mitral stenosis have been reported by Wood [*24*], and by Musser, Bougas and Goldberg [*25*].

The aortic valve flow in the patients with severe aortic stenosis combined with mitral

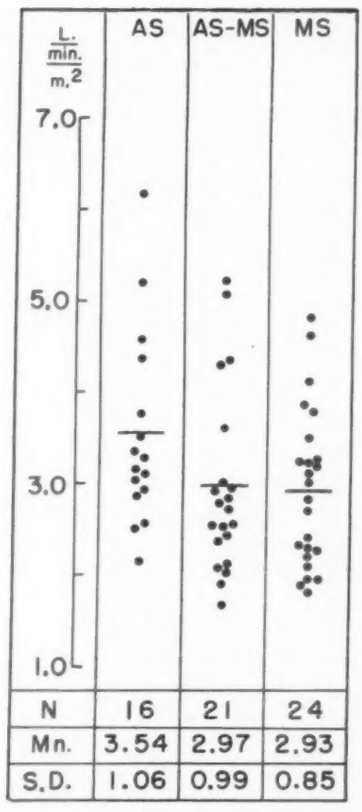


FIG. 4

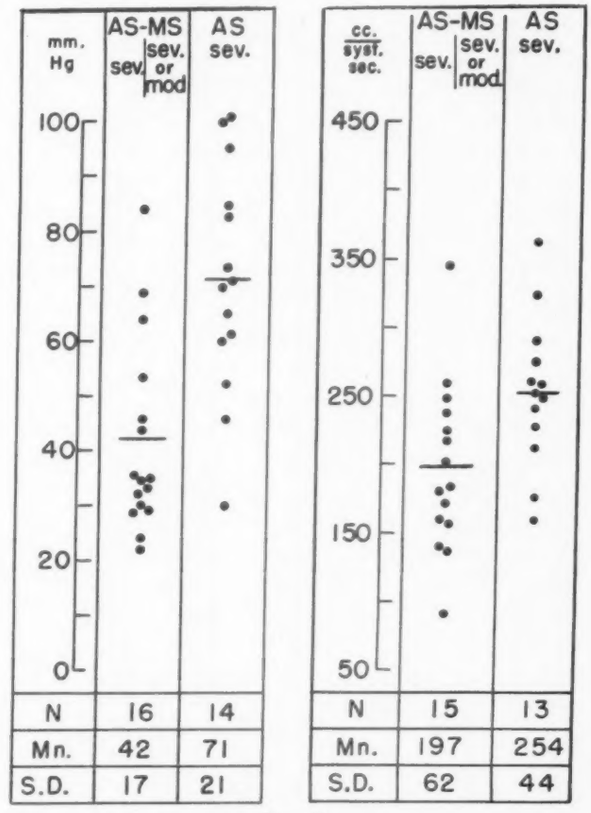


FIG. 5

FIG. 4. Cardiac index in solitary aortic stenosis (AS), combined aortic and mitral stenosis (AS-MS) and solitary mitral stenosis (MS).

FIG. 5. Mean pressure gradient and flow across the aortic valve (A.V.) in severe aortic stenosis combined with severe or moderate mitral stenosis, and in solitary severe aortic stenosis.

stenosis (197 cc./systolic second, standard deviation 62) was lower ($p < 0.05$) than in those with solitary severe aortic stenosis (254 cc./systolic second, standard deviation 44). These relationships still obtained when flow was expressed per unit of body surface area. Thus for a given aortic valve area both the gradient and the flow across the aortic valve were lower in the presence of significant mitral stenosis.

Pressure Gradient and Flow Across the Mitral Valve (*Fig. 6*). The diastolic pressure gradient across the mitral valve in combined stenosis averaged 12 mm. Hg. The mean mitral valve flow was 173 cc./diastolic second. Gradient and flow were not significantly different in combined stenosis and in solitary mitral stenosis.

Left Ventricular Work (*Fig. 7*). The total left ventricular work determined in this laboratory by left heart catheterization in eight patients without heart disease was 5.27 kg. M./min./sq. M., standard deviation 0.94. The total left ventricular work in solitary aortic stenosis (7.22 kg. M./min./sq. M., standard deviation 2.51) was approximately one and one-third times that of the entire combined group (5.59 kg. M./min./sq. M., standard deviation 2.78) and twice that of the mitral stenosis group (3.67 kg. M./min./sq. M., standard deviation 1.28). It is noteworthy that the total left ventricular work in solitary severe aortic stenosis (7.01 kg. M./min./sq. M., standard deviation 1.31) was significantly higher ($p < 0.01$) than in the group with severe stenosis at both valves (3.87 kg. M./min./sq. M., standard deviation 0.87) and in the group with solitary severe mitral stenosis (3.09 kg. M./min./sq. M., standard deviation 0.63). Furthermore, the work of the left ventricle in the patients with severe aortic stenosis combined with moderate mitral stenosis was 6.95 kg. M./min./sq. M., standard deviation 1.09, nearly twice that of the patients with severe aortic stenosis combined with severe mitral stenosis ($p < 0.01$). The work of the left ventricle in the group with solitary moderate

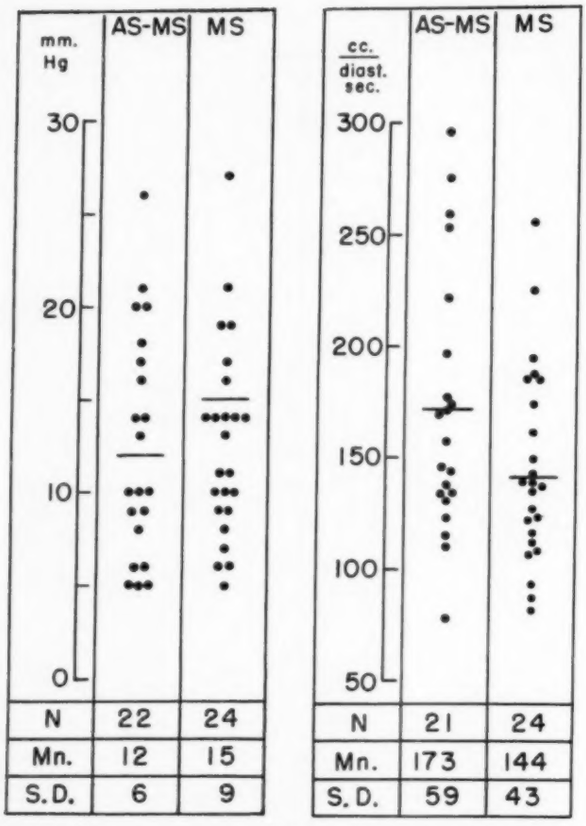


FIG. 6. Mean pressure gradient and flow across the mitral valve (M.V.) in combined aortic and mitral stenosis compared to solitary mitral stenosis.

mitral stenosis was intermediate (4.91 kg. M./min./sq. M., standard deviation 1.45).

Left Ventricular and Left Atrial Pressures. High left ventricular systolic pressures were maintained usually without elevation of the left ventricular end-diastolic pressure. Left ventricular end diastolic pressure was above 10 mm. Hg in only 18 per cent in contrast to 65 per cent in solitary aortic stenosis. This difference has also been reported by Musser et al. [*25*]. Mean left atrial pressures averaged 20 mm. Hg in combined stenosis and in solitary mitral stenosis, and 11 mm. Hg in solitary aortic stenosis.

Arterial Pressure Contour. Almost all nineteen brachial artery pressure tracings were abnormal in form. The upstroke was greater than 0.14 second in all but one (Case 21), and an anacrotic notch was present in all except three patients (Cases 4, 19 and 20). Severity of aortic stenosis could not be judged by these alterations in arterial pulse contour. These findings are comparable to those in solitary aortic stenosis [*26*].

Pulmonary Hypertension. Pulmonary vascular pressures were measured in twelve patients. Pulmonary hypertension was present in the six patients with severe aortic and severe mitral stenosis and in four of the remaining six. The mean total pulmonary resistance was 500 dynes sec. cm.$^{-5}$, and the mean pulmonary arteriolar resistance was 217 dynes sec. cm.$^{-5}$, both elevated. The total pulmonary resistance was increased in all patients in the combined group with severe mitral stenosis (mean 746 dynes sec. cm.$^{-5}$). Of the four in whom the total pulmonary resistance was greater than 640 dynes sec. cm.$^{-5}$, the left ventricular end diastolic pressure was

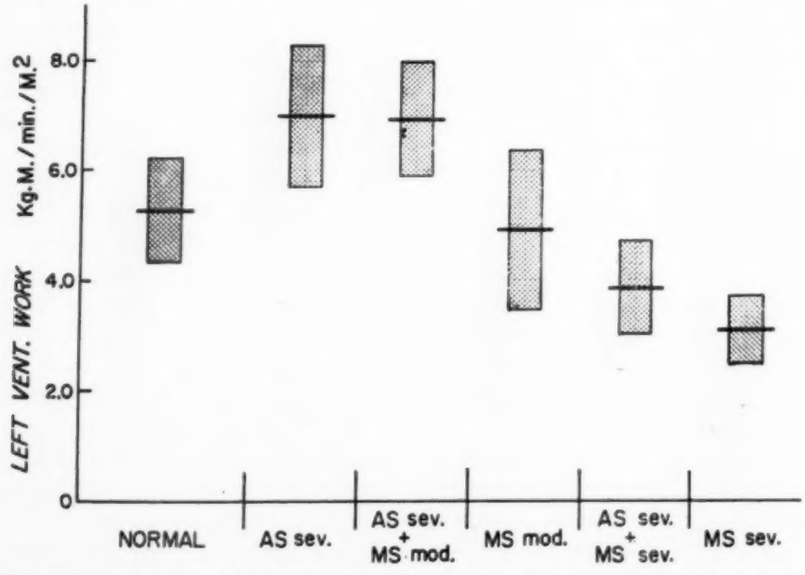


FIG. 7. Total left ventricular work in aortic stenosis, combined stenosis and mitral stenosis. For each group, the mean ±1 standard deviation is indicated.

above 10 mm. Hg in two. Thus, elevation of the left ventricular diastolic pressure, the mitral valve pressure gradient and the pulmonary vascular resistance each contributed to the increased total pulmonary resistance.

Right Ventricular Failure. Signs of right ventricular failure at the time of initial examination were present in six patients: distention of neck veins and peripheral edema were present in all six, hepatomegaly in three and pleural effusion in two. Four of these patients were symptomatic at rest. All had severe aortic stenosis, which was associated with severe mitral stenosis in three and moderate mitral stenosis in three. Catheterization following maximal medical therapy revealed a low cardiac index in three of six, an elevated right ventricular end-diastolic pressure in three of four and a high pulmonary vascular resistance in two of three.

COMMENTS

Certain features of combined aortic and mitral stenosis were modified by their coexistence. The most common alteration in the signs of mitral stenosis was the relative infrequency of the accentuated M_1, the opening snap and the diastolic murmur. The occasional absence of one or all of these signs in patients with solitary mitral stenosis [*22*] has been attributed to factors such as excessive calcification or poor mobility of the valve [*27,28*]. Such factors could not be demonstrated to be more operative in the patients with combined stenosis.

The implication of these findings, however, is clear. The absence of the auscultatory signs of mitral stenosis does not exclude the presence of this lesion in patients with evident aortic stenosis. The features suggesting coexistent mitral stenosis in patients with stenosis of the aortic valve are atrial fibrillation or P-mitrale, and radiologic evidence of left atrial enlargement, right ventricular enlargement and presence of calcification of the mitral valve. It must be remembered, however, that in solitary aortic stenosis atrial fibrillation may occur, albeit as a late phenomenon [*21,29*], and enlargement of the left atrium and right ventricle may also be present.

When the apical diastolic murmur is the only manifestation of mitral stenosis, it may be misinterpreted as an Austin Flint murmur. In our experience and that of others [*30*], however, an Austin Flint murmur is unlikely unless there is massive enlargement of the left ventricle.

The clinical history of patients with the combined lesion, unlike the signs, may more often favor the diagnosis of mitral stenosis: women predominate, and symptoms develop relatively earlier and tend to be more chronic in course than in solitary aortic stenosis. Palpitation, hemoptysis and systemic emboli, common in isolated mitral stenosis, are frequent.

In contrast, certain symptoms of aortic stenosis were infrequent, notably angina, dizziness and syncope. Auscultatory signs of aortic stenosis were preserved, but some signs usually considered indicative of severe aortic stenosis, such as a left ventricular thrust and a small, slowly ascending peripheral pulse, were not consistently present. In addition, less common in the patients with combined stenosis were the fluoroscopic findings of calcification of the aortic valve and poststenotic dilatation of the ascending aorta, and electrocardiographic evidence of left ventricular hypertrophy. A lower incidence of the features of aortic stenosis in patients with combined stenosis has also been reported in the literature [*21,31*].

The cardiac output was low in the group with combined aortic and mitral stenosis, similar to that in solitary mitral stenosis and lower than in solitary aortic stenosis. Thus the size of the mitral orifice is a determinant of flow. In mitral stenosis, the maximum flow is determined by the pressure which can be reached in the left atrium before pulmonary edema occurs. In addition, when the left ventricular diastolic pressure is elevated, as may occur in aortic stenosis, the maximum gradient and, therefore, the maximum flow are further limited. Thus the effect of mitral stenosis on the heart with aortic stenosis is to lower the flow and the pressure gradient across the aortic valve, with a resultant decrease in left ventricular work. Indeed, the total left ventricular work was significantly lower in combined aortic and mitral stenosis than in solitary aortic stenosis; it was also lower in isolated mitral stenosis than in the normal (Fig. 7). This effect of mitral stenosis could be demonstrated only when the lesion was severe.

The diminished left ventricular work in combined aortic stenosis as compared to solitary aortic stenosis may be the physiologic basis for the decreased incidence of angina, and of left ventricular hypertrophy and failure. Increased velocity of aortic flow has been incriminated as a factor reducing coronary flow in aortic stenosis [*32*]. The relatively lower velocity of aortic flow

in the combined group may also play a direct role in the reduced incidence of angina in these patients. In addition, the lower incidence of post-stenotic dilatation of the ascending aorta may be related to lower pressure and lower velocity of flow in the patients with combined stenosis as compared to those with solitary aortic stenosis [*33*].

Physiologic observations were not made during exercise. However, mitral stenosis has been shown to limit the response of cardiac output to exercise [*12*]. Therefore, the limiting effect of mitral stenosis on the gradient across the aortic valve and on left ventricular work may be expected to be accentuated during exercise.

The possibility that mitral stenosis spares the left ventricle has been suggested by others [*18,25,34*]. D'Allaines and Herrero [*18*] postulated that in patients with combined stenosis the mitral lesion "protects" the left ventricle from undue work and hypertrophy. Noteworthy are the observations of Bailey and associates [*31*] who described the left ventricle in patients with combined stenosis to be smaller, firmer and less irritable than in patients with aortic stenosis.

Following the onset of symptoms the prognosis in patients with aortic and mitral stenosis is more favorable than in patients with aortic stenosis alone. This has also been reported by others [*17,19*]. The rapid progression of symptoms and the sudden deaths characteristic of the patients with solitary aortic stenosis appear to be less common [*21,29,35*].

Inasmuch as the onset of symptoms in patients with combined stenosis is likely to be earlier than with aortic stenosis alone, the life expectancy in the former may in fact be less [*17,19,21*]. No conclusions can be reached in this regard from the present study since follow-up was limited.

An accurate clinical diagnosis of the type of valve disease can usually be made in stenosis of a single valve. However, although clinical assessment of the severity of the lesion is usually correct in solitary mitral stenosis [*36*], assessment of the severity of solitary aortic stenosis is more difficult [*37*]. The data presented indicate that there is difficulty in the clinical estimation of both type and severity of the valve lesions in combined stenosis. If an accurate diagnosis is to be made, catheterization of the left side of the heart with simultaneous measurement of pressure and flow across each valve must be performed. Measurement of pressure gradients alone is unsatisfactory, particularly in view of the relatively low pressure gradient and flow across the aortic valve in patients with combined stenosis. Catheterization of the right side of the heart, in addition, permits evaluation of the tricuspid valve.

SUMMARY AND CONCLUSIONS

Twenty-two patients with combined aortic and mitral stenosis were studied clinically and physiologically. Comparisons were made with a group of seventeen patients with significant solitary aortic stenosis and a group of twenty-four patients with significant solitary mitral stenosis.

Certain clinical features of aortic and mitral stenosis were modified by their coexistence. (1) The natural history of combined stenosis was dominated by features of mitral stenosis: females predominated; symptoms began at an early age; duration of symptoms was chronic; and prognosis, once symptoms occurred, was more favorable than in patients with solitary aortic stenosis. Although none of the symptoms common in mitral stenosis was altered by the combination, certain features of aortic stenosis, notably angina, dizziness and syncope were infrequent. (2) The physical signs of aortic stenosis were usually present. However, radiologic and electrocardiographic features were often absent. Infrequent were the small, slowly ascending peripheral pulse, calcification of the aortic valve, poststenotic dilatation of the ascending aorta and electrocardiographic evidence of left ventricular hypertrophy, usually reliable indices of severe aortic stenosis. In contrast, the physical signs of mitral stenosis were often absent, but the radiologic signs were evident.

Mitral stenosis, when severe, limited cardiac output, resulting in a lower pressure gradient across the aortic valve and thus in a decrease in the work of the left ventricle. This may explain the decreased incidence of some of the features of aortic stenosis in the combined lesion.

The clinical evaluation of combined aortic and mitral valve disease is difficult. Catheterization of the left side of the heart with measurement of pressures and flows across both valves permits accurate assessment of the lesions.

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Renal Cortical Necrosis*

Clinical and Pathologic Features in Twenty-One Cases

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CORTICAL necrosis of the kidneys, a relatively rare condition, was found at necropsy in thirteen patients at the Cincinnati General Hospital in a period of only seventeen months (September 1955 through January 1957). Nearly sixty patients with acute renal failure of varying causes were observed during this same period; those with proved cortical necrosis, then, represent more than 20 per cent of this group. These thirteen cases and others culled from the files of the Department of Pathology have been studied in detail to correlate clinical and pathologic findings and to attempt to explain this unusual frequency of the entity.

Renal cortical necrosis in man is a distinct pathologic entity, the genesis of which is unknown. It is characterized by a variable extent of necrosis confined to the cortical portions of the kidneys, including the columns of Bertini. The first reported case was by Juhel-Rénoy in 1886 [*1*]. Ash in 1933 [*2*] found only sixty cases recorded in the entire medical literature and in 1949 Haft [*3*] estimated that approximately 100 cases had been reported. Probably less than 160 cases have appeared in the medical literature to date.

CASE MATERIAL

Twenty-one cases of renal cortical necrosis serve as the basis of this study. These include the thirteen already cited. Since 1953, twenty instances have been encountered at necropsy at the Cincinnati General Hospital. Sixteen of the twenty patients were regular hospital admissions and thus indigenous to the hospital population. Four patients were transferred from other hospitals for hemodialysis. The remaining patient† was hospitalized at the Cincinnati Children's Hospital. There were three cases in each of the three years of 1953, 1954 and 1955, six cases in 1956 and one in January 1957 at the Cincinnati General Hospital. The remaining five cases from other hospitals all were seen during 1956 and early 1957.

† We are indebted to Dr. Clark West for permission to include this case in the present report.

CLINICOPATHOLOGIC OBSERVATIONS

The age range in the twenty-one patients was from ten months to eighty-two years. (Table I.) There were fifteen females and six males.

Pre-existing and Associated Conditions. The development of cortical necrosis in these patients was associated with a wide variety of clinical disorders. (Table I.) Extensive second and third degree burns were present in three patients. An additional three patients had upper gastrointestinal hemorrhage, from a peptic ulcer in two and from a malignant lymphoma of the stomach in the third. One of the patients with peptic ulcer also had a carcinoma of the tonsil, while the patient with lymphoma also had multiple myeloma, carcinoma of the prostate, acute hemorrhagic enterocolitis and acute generalized peritonitis. Three patients had acute peritonitis, two due to perforated peptic ulcer and one due to shotgun wound with multiple visceral perforations.

There were three instances accompanying pregnancy, all with abruptio placentae. Pituitary necrosis also was found in the two of these patients in whom examination of the brain was made. Two patients had head injuries, one with bilateral subdural hematomas and the other with facial bone fractures and lacerations.

Two patients had severe acute pulmonary insufficiency. Of these, one had pulmonary fibrosis related to extensive pulmonary metastasis from prostatic carcinoma. This patient also had multiple cerebral thrombi. The other patient had a large pulmonary embolus following bilateral ligation of femoral veins for thrombophlebitis. This patient also had metastasis to

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TABLE 1
PRE-EXISTING AND ASSOCIATED CONDITIONS
Twenty-one Cases of Cortical Necrosis

Case No.	Age (yr.) and Sex	Days of Anuria/ Oliguria	Major Associated Illness	Remarks	
1	69, F	4	2nd and 3rd degree burns	23% of body surface	...
2	65, F	2	2nd and 3rd degree burns	50% of body surface	...
3	36, M	7	2nd and 3rd degree burns	45% of body surface	...
4	82, F	1(?)	Gastrointestinal hemorrhage	Chronic gastric ulcer	n1
5	73, F	7	Gastrointestinal hemorrhage	Acute gastric ulcer	...
6	70, M	2	Gastrointestinal hemorrhage	Malignant lymphoma of stomach	n2, s1
7	63, M	12	Peritonitis	Perforated marginal gastrojejunal ulcer	n3
8	75, M	5	Peritonitis	Perforated gastric ulcer	s2
9	26, F	6	Peritonitis	Multiple perforations of stomach, duodenum and gallbladder; shot gun wounds	...
10	40, F	31	Abruptio placentae	Multipara	s3
11	44, F	19	Abruptio placentae	Multipara	...
12	32, F	3 (+14)	Abruptio placentae	Multipara	s4
13	40, F	9	Trauma to head	Facial bone fractures and lacerations with division of left facial nerve	s5
14	41, F	10+	Trauma to head	Bilateral subdural hematomas	...
15	70, M	4	Pulmonary insufficiency	Metastatic carcinoma of lungs	n4
16	61, F	1(?)	Pulmonary insufficiency	Pulmonary embolus, massive	n5, s6
17	62, F	1	Bile duct carcinoma	Obstructive jaundice	n6, s7
18	60, M	6	Abdominal aortic aneurysm	Resected; patent vessel homograft	s8
19	38, F	21	Chronic skin ulceration of left groin, self-induced	Blood transfusion 2 days before renal shutdown	s9
20	10 mo., F	14	Diarrhea and dehydration	Microcephaly	...
21	49, F	15	None	Nocturia for 3 months	...

NOTE: n = neoplasm:
n1: carcinoma of tonsil with pulmonary metastasis.
n2: carcinoma of prostate, malignant lymphoma and multiple myeloma.
n3: carcinoma of prostate.
n4: adenocarcinoma of prostate with pulmonary metastasis.
n5: carcinoma of breast with pulmonary metastasis.
n6: carcinoma of bile ducts.
s = surgery:
s1: total gastric resection.
s2: laparotomy and closure of perforated peptic ulcer.
s3: cesarean section.
s4: cesarean section.
s5: repair of facial lacerations and nerve.
s6: bilateral femoral vein ligation.
s7: common duct exploration.
s8: resection of aortic aneurysm and transplant of vessel homograft.
s9: pinch grafts to skin ulceration.

the lungs, pleura and lymph nodes from carcinoma of the breast.

One patient had obstructive jaundice due to carcinoma of the bile duct with infiltration of the liver and massive hepatic necrosis. In another instance renal cortical necrosis occurred immediately after resection of an abdominal aortic aneurysm. At necropsy the vessel homograft was intact and the major renal arteries and veins were patent. In another patient cortical necrosis developed while being treated for a chronic and probably self-induced skin ulceration in the left inguinal region. The ten month old infant with cortical necrosis had a three-day history of fever, diarrhea and marked dehydration. One patient who had no obvious precipitating cause for renal failure had complained only of nocturia for a three-month period; marked thrombocytopenia

TABLE II
CLINICAL OBSERVATIONS
Twenty-one Cases of Cortical Necrosis

Clinical Observations	Positive Occurrence of Total Examined	Remarks
Hypotension immediately prior to renal failure	15/18	Blood pressure not measured with onset of renal failure (3)
Hypertension preceding cortical necrosis	4/21	Benign essential
Hypertension during course of renal failure	7/21	Pre-existing hypertensive disease (2), accelerated hypertension developed in 1*
Terminal shock	12/12	Blood pressure not measured terminally (9)
Abdominal/flank pain	12/15	Could not be evaluated (6)
Accurately measured urinary output	15	...
Total anuria†	12	...
Total anuria absent	3	Focal patchy, or less than 50% cortical necrosis on histological study
Severe oliguria‡	14	...
Microscopic hematuria	14/14	During course of renal failure
Gross hematuria	6	All included in group with microscopic bleeding

* Pituitary necrosis found at necropsy.
† For one or more days.
‡ Less than 50 cc./day for half or more of the course of renal failure.

and hypoprothrombinemia developed during the course of her illness.

Surgical procedures were performed on nine of the twenty-one patients during their hospital course prior to development of the fatal renal lesions. Six of the nine operations were major procedures. (Table I.)

Six patients had malignant neoplasms. (Table I.) Also, four patients had peptic ulcers, three of which were benign gastric ulcers and one a perforated gastrojejunal marginal ulcer with a gastrocolic fistula.

Eighteen of the twenty-one patients had evidence at necropsy of infection in a wide variety of locations. These included lung, peritoneal cavity, biliary tree, genitourinary tract and skin. All patients in the series had fever and leukocytosis. Blood cultures during life were obtained in only five instances and in none of these was there bacterial growth.

Blood Pressure. Hypotension occurred prior to the development of renal failure in fifteen of the eighteen patients in whom blood pressure was measured. (Table II.) The hypotension persisted until death in four of these patients, none of whom survived more than four days. All twelve patients in whom blood measurements were recorded during the terminal portion of their illness died in shock.

Hypertension developed during the course of acute renal failure in seven patients. The diastolic pressures ranged from 90 to 150 mm. Hg. Two of the seven were known to have had pre-existing hypertensive disease. In one patient (Case 12, to be more fully described subsequently) accelerated hypertension developed suddenly as manifested by bilateral retinal hemorrhages and a rise in blood pressure from 155/80 to 220/100 mm. Hg on the fifth day of oliguria.

Pain. Pain in the abdomen or flanks was present in twelve of the fifteen patients in whom this symptom could be evaluated. (Table II.) In four patients the pain appeared to be related solely to the renal lesion. Two of the four had gross hematuria. In the other eight, pain could have been due to the associated illness rather than to the renal involvement *per se.*

Urinary Findings. Accurate measurement of daily urinary output was recorded in fifteen patients. (Table II.) Total anuria (complete absence of urine) occurred in twelve patients; the duration was two to seven days in nine patients and less than two days in three. The remaining three patients who never exhibited total anuria were later shown histologically to have had involvement of 50 per cent or less of the renal cortices by the pathologic process, and therefore are distinguished on clinical and pathologic grounds from the rest of the patients of this series.

TABLE III
THERAPY
Twenty-one Cases of Cortical Necrosis

Therapy	No. of Patients	Remarks
		Before Renal Shutdown
Whole blood transfusions	16	No known transfusion reaction
Plasma	3	...
Antibiotic therapy	6	...
Steroids	0	...
Pressor drugs	9	Norepinephrine (3); ergotrate and oxytocin (3); ephedrine (1); phenylephrine (1); methoxamine (1)
Tetanus antitoxin	5	...
		After Renal Shutdown
Whole blood transfusions	11	No known transfusion reaction
Plasma	0	...
Antibiotic therapy	21	All but 1 patient received two or more antibiotics
Steroids	5	Prednisone (1); hydrocortisone (4)
Pressor drugs	9	Norepinephrine (7); norepinephrine and phenylephrine (1); norepinephrine and methoxamine (1)
Hemodialysis	8	Dialyses (12); 4 patients dialyzed twice
		Before and After Renal Shutdown
Whole blood transfusions	17	...
Plasma	3	...
Antibiotic therapy	21	...
Steroids	5	...
Pressor drugs	14	...

Severe oliguria, amounting to less than 50 cc. of urine per day for at least one-half of the hospital course, occurred in fourteen of the fifteen patients. The single patient who did not have severe oliguria had only focal cortical necrosis at necropsy.

Hematuria was found in fourteen patients in whom microscopic examinations of the urine were made during the period of renal insufficiency. Grossly bloody urine was recorded early in the course in six patients.

Factors of Therapy. Table III outlines the therapy administered prior to and during the time of oliguria. Whole blood or plasma transfusions were given to nineteen patients in the course of treatment of the associated illnesses before the appearance or recognition of renal failure. In seventeen patients oliguria developed within forty-eight hours of the time these infusions were given. In one patient (Case 4) the renal shutdown developed five days after transfusion. Another patient (Case 14) received only plasma, and the period between this infusion and the development of renal failure is unknown. One patient's blood transfusions were given only after onset of renal failure. Ten of the nineteen patients continued to receive transfusions during the period of renal shutdown.

Six patients received antibiotic therapy before any renal disorder was evident. All twenty-one patients were treated with chemotherapeutic agents during the course of renal failure. Penicillin was given to nineteen patients and was used with at least one other antibiotic drug in eighteen. Ten patients received one of the tetracycline drugs; nine of these also received at least one other antibiotic agent. Streptomycin with penicillin was used in nine patients. Chloramphenicol was given to four patients and sulfisoxazole to three. Neomycin and erythromycin each were used in one instance. Bacitracin ointment was applied to an ulcerated skin lesion in one patient.

TABLE IV
PATHOLOGY OF KIDNEYS
Twenty-one Cases of Cortical Necrosis

Case No.	Gross Appearance of Cortical Necrosis	Microscopic Evaluation		
		Amount of Cortical Necrosis (%)	Pre-existing Renal Disease	No. of Sections
1	Massive	80	Severe chronic pyelonephritis*	3
2	Massive	<50	Slight arteriolosclerosis; moderate chronic pyelonephritis*	2
3	Massive	100	Pyelonephritis	1
4	Massive	Almost total	None	2
5	Massive	100	Moderate arteriolosclerosis	4
6	Massive	90	Moderately severe arteriolosclerosis	3
7	Not characteristic	10	Slight arteriolosclerosis; moderate chronic pyelonephritis*	5
8	Massive	85 (one kidney) 30 (other kidney)	Moderate arteriolosclerosis; moderate chronic pyelonephritis*	2
9	Massive	100	None	2
10	Massive	75	Severe arteriolosclerosis; membranous glomerulonephritis†	5
11	Massive	Almost total	Large vessel sclerosis	2
12	Patchy	15	Severe tubulorhexic nephrosis; no pre-existing disease	2
13	Massive	98	None	2
14	Massive	Almost total	Severe arteriolosclerosis	2
15	Massive	>90	Moderate large vessel sclerosis; chronic pyelonephritis‡	2
16	Massive	100	None	1
17	Massive	100	None	1
18	Massive	>90	Moderate arteriolosclerosis	1
19	Massive	>95	None	4
20	Massive	95	None	2
21	Massive	80	Minimal arteriolosclerosis	4

* Active.
† Subacute and chronic.
‡ Inactive.

Tetanus antitoxin was administered to five patients, none of whom manifested sensitivity reactions.

Fourteen of the twenty-one patients received oxytocic or pressor drugs during the course of their illnesses. (Table III.) Five of the fourteen patients received these drugs prior to renal failure only; five received a pressor drug sometime during the course of renal failure; and four had pressor therapy both before and after renal shutdown. Corticosteroids were administered unsuccessfully to five patients late in the course of renal failure. The use of hydrocortisone in three cases was uniformly unsuccessful in correcting hypotension. A fourth patient received hydrocortisone for three days in an attempt to correct a bleeding diathesis associated with thrombocytopenia. One patient was given prednisone on the last six days of life because the diagnosis of hypersensitivity angiitis was entertained.

Hemodialysis was performed in eight patients (four patients had dialysis performed twice) to ameliorate uremic symptoms, acidosis and potassium intoxication, and to support the patients during the period of acute renal failure.

Duration of Life. Survival of these twenty-one patients, from the time of recognition of renal failure to the fatal termination, varied from one to thirty-one days. (Table I.) Twelve patients died within one week of the onset of renal failure, usually of the associated illness. Only five patients lived longer than two weeks; each of these required hemodialysis in addition to more conservative measures of treatment of acute renal failure. Survival for even longer periods of time has been reported in several patients [*4,5*] who subsequently died of renal failure.

Pathologic Findings in the Kidneys. Table IV summarizes the pathologic observations in the kidneys of this group of patients. Gross examina-

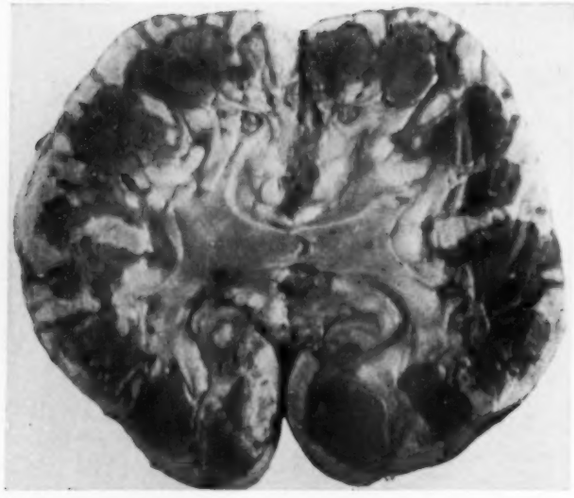


FIG. 1. Case 11. Gross appearance of massive cortical necrosis in patient with abruptio placentae. Note the coagulative appearance of almost the entire cortical tissue and parts of the columns of Bertini.

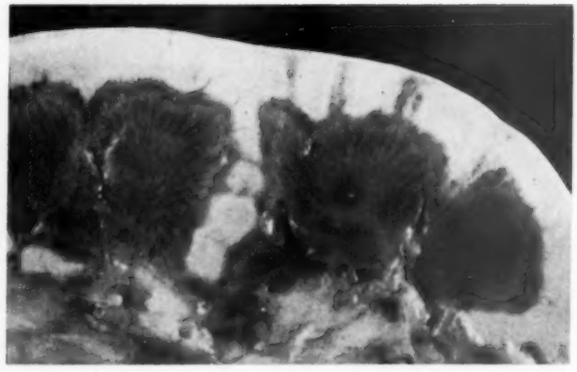


FIG. 2. Close-up of part of kidney seen in Figure 1. In this particular view the usual subcapsular area of intact cortical tissue is not demonstrated.

tion of the kidneys in all but two revealed the typical appearance of massive bilateral cortical necrosis (Figs. 1 and 2) characterized by sharply demarcated pallid necrosis of the renal cortex and contiguous columns of Bertini, no involvement of the renal pyramids and of a thin rim of subcapsular tissue, and a narrow hemorrhagic zone usually outlining the necrotic areas.

The extent of necrosis was estimated roughly from the gross appearance and from the available microscopic material. One to five microscopic sections of kidney were studied in each patient. In eighteen of the twenty-one patients the extent of necrosis of the cortex ranged from 75 to 100 per cent (arbitrarily defined hereinafter as "massive"). In one patient (Case 2) microscopic study exhibited less than 50 per cent involvement of the cortex although the gross appearance simulated massive cortical necrosis. In two patients (Cases 7 and 12) with only 10 and 15 per cent destruction of the cortex the gross appearance was not that of massive necrosis.

Pre-existing renal abnormality, usually chronic pyelonephritis or nephrosclerosis, was found in the kidneys of fifteen of the twenty-one patients. These findings are recorded in Table IV.

COMMENTS

Cortical necrosis may occur at any age, the range in the present series being ten months to eighty-two years. The disorder has been reported in a one month old child [*6*] and an instance has been encountered in an infant only a few days old born under circumstances of abruptio placentae [*7*]. There is said to be no difference in incidence between the sexes when obstetrical cases are excluded [*8*]; however, twelve of the eighteen non-obstetrical cases in the present series were female.

Consideration of Etiological Factors. Although a variety of conditions may antedate the development of renal cortical necrosis, complications of pregnancy are generally emphasized as the initiating factors in from 50 [*3*] to 80 per cent [*9*] of the cases. The current series differs in that only three of the twenty-one cases occurred in association with pregnancy. The reason for this disproportionate incidence of non-obstetrical conditions is not apparent. Major surgical procedures, burns, gastrointestinal hemorrhage and generalized peritonitis were of equal frequency (three cases each). Of special note is that six of the twenty-one patients had malignant neoplasms of varied types. Every patient in the group had some clinical evidence of one or another disease antedating the development of cortical necrosis, although in one patient (Case 21) this evidence was very slight.

Nineteen of the twenty-one patients received either blood or plasma prior to the development of renal failure, but no transfusion reactions were observed. One case has been reported in which cortical necrosis followed a transfusion reaction [*10*]; however, doubt has been cast upon any such relationship by one author [*9*]. Administration of blood and plasma to so many of these patients was probably coincidental to the development of the fatal renal lesion and merely reflected the frequency of hypotension and blood loss in these cases. Although in two of the pa-

tients mismatched transfusions may conceivably have been contributory, proof of this was not manifest. One patient (Case 19) with chronic malnutrition and a large non-healing ulcerated area in the left groin received a blood transfusion for anemia two days before the onset of irreversible oliguria. Although there was no reaction to this blood, which was apparently properly cross matched, the possibility does exist that the pathologic changes of the kidneys may have been initiated by the transfusion. The other patient (Case 2) was a sixty-five year old woman who suffered a burn of 50 per cent of her body surface. The early part of her course, during which time transfusions were frequently administered, was uncomplicated and normal urinary excretion was maintained. On the fifth day jaundice and severe oliguria developed, and she died two days later. Necrosis, affecting less than 50 per cent of the renal cortex, was found at necropsy. Because of the lag period between the burn and the onset of renal failure it is possible that a mismatched transfusion could have been responsible for the cortical necrosis in this instance.

Although infection was present in most patients in the group, it is not clear what role this might have played in the production of renal necrosis. It is improbable that the pathologic alterations in the kidneys were due to the direct invasion of bacteria. Although the toxins of bacteria have been used experimentally to induce cortical necrosis [*6,11,12*], the absence of an unusual incidence of one type of infection or of a particular site of involvement in this series probably militates against an essentially toxic mechanism. Also, the antibacterial agents utilized are probably not responsible, for none have heretofore been reported to produce any such lesions.

Other therapeutic agents used in these patients have been scrutinized for their possible role in the production of this condition. Corticosteroids have been used experimentally to predispose animals receiving bacterial toxins to the development of cortical necrosis [*12*]. Although five of the twenty-one patients received steroids, these were administered late in the course of renal failure, and therefore could not have initiated the process. What effect these adrenal steroids might have had on the progression and extent of renal cortical necrosis is unknown. The same problem is raised in the use of pressor and vasoconstrictor agents, in that oxytocin [*13*], epinephrine [*14*] and serotonin [*15*] have all been utilized to produce cortical necrosis in the experimental animal. In the present series fourteen patients received pressor drugs, mostly norepinephrine, at some time during the course of hospitalization. Boughton and Sommers [*16*] describe pathologic alterations similar to the "proximal tubular necrosis" with "focal cortical necrosis" of Sheehan and Moore [*17*] in the kidneys of eight patients, whose shock was treated vigorously with norepinephrine. Spasm of the renal vasculature intensified by therapy with norepinephrine was believed to be a major contributory factor. The possible role of these agents in the present series cannot be overlooked. None of the other medications used in these patients was considered to have significant import.

Neoplastic lesions appeared with notable frequency among these patients. The primary sites of origin were prostate (three cases), tonsil, breast and biliary ducts. One patient had three separate malignant lesions (gastric lymphoma, carcinoma of the prostate and plasmocytic myeloma). In three patients the carcinomatous lesions had metastasized to the lungs.

The fact that nine patients had experienced surgical operations prior to development of renal shutdown, six of these being major operations, raises the question of the relationship of cortical necrosis to trauma. Again, this high incidence would appear merely to reflect the severity and range of the associated illnesses, for there is no evidence that surgical manipulation, *per se*, is directly responsible for the production of the renal process. Only one patient (Case 21) in this group had been subjected to retrograde pyelography; this procedure was performed two days after the onset of anuria.

Hemodialysis has been employed in many severely ill patients with anuria and oliguria, and in no series has any significant number of cases of renal cortical necrosis been noted. Eight of the present patients were treated by dialysis, in each instance with the hope that the anuria would be temporary and reversible. It is unlikely that the dialysis itself contributed to the irreversible oliguria. The question is posed whether destruction of platelets during the procedure could cause release of sufficient amounts of serotonin to aggravate or, indeed, to produce a renal lesion of this magnitude.

The cause of renal cortical necrosis remains unknown. The single common factor which is

apparent in nineteen of the twenty-one patients of this series is renal ischemia due to renal vasoconstriction such as may accompany systemic hypotension, pressor drug administration, hemorrhage, bacterial infection, surgery and anesthesia, or extensive burns of body surface. Many authors have speculated that prolonged or intense renal vasoconstriction could be the cause of cortical necrosis. It is readily apparent that the associated diseases in the present group of patients are not unlike those recorded in large series of patients with acute tubular necrosis (lower nephron nephrosis or tubulorhexic nephrosis), a condition also generally believed to have its origin in renal ischemia [*18*]. However, although tubulorhexic nephrosis and cortical necrosis may be closely related in pathogenesis [*6*], it is not possible to estimate from the present experience which pathologic lesion will result from which particular challenge.

In the experience of these seventeen months with sixty instances of acute renal failure, massive cortical necrosis developed in one-fifth of the patients. There is the plaguing possibility that the renal shutdown in these patients may have been due at the outset to tubulorhexic nephrosis, and that cortical necrosis may have developed during the period of oliguria. For the purpose of the present analysis it has been inferred from the demonstration of fully developed typical cortical necrosis in patients who died within forty-eight hours of development that in all patients with cortical necrosis at necropsy this pathologic lesion must have developed with the onset of clinical manifestations of renal shutdown. However, one patient (Case 12) may be an exception, cortical necrosis possibly having developed late in the course of renal shutdown. This patient was anuric following a delivery complicated by abruptio placentae, afibrinogenemia and shock. During the seven days of anuria rapidly advancing hypertension of malignant character developed. Subsequently, although urinary excretion increased daily, the patient failed to improve clinically and showed no chemical evidence of remission. Seventy-two hours before death there was an unexplained episode of shock, after which anuria recurred. At necropsy, minimal cortical necrosis was observed and there were also healing tubulorhexic nephrosis and membranous glomerulonephritis. The latter was consistent with that observed in eclampsia. Although toxemia of pregnancy was an important part of the clinical picture, the patient first manifested renal shutdown in keeping with the tubulorhexic nephrosis seen at necropsy. It is highly probable that the superimposed minimal cortical necrosis could have been induced by the preterminal period of shock, for it appeared to be of recent origin and of minor consequence in terms of total renal functional impairment. Infarction of the anterior pituitary was also present in this case. The existence of cortical necrosis, albeit of minor degree, and the fact that this lesion is so commonly associated with abruptio placentae warrants retention of this case in the present survey.

Evaluation of Pathologic Findings. It is believed that the pathologic estimation of the degree of involvement of the renal cortices in this series is reasonably accurate, even in the situations in which only one or two microscopic sections were studied, since the estimate noted by gross appearance regularly confirmed that obtained by microscopy. Eighteen of the twenty-one patients had massive, i.e., more than 75 per cent, cortical necrosis. In these instances it was apparent that the remaining renal tissue was insufficient to support life. Prognosis, then, must certainly have been fatal from the outset. However, in the other three patients recovery from renal failure may have been possible, as in selected instances noted in the literature [*5,9,19–21*]; for in these three patients the associated conditions (severe peritonitis, infarction of the pituitary and extensive burns of the body surface) were probably the immediate causes of death. It is noted that the urinary output in these three patients was greater than the "total anuria—50 cc. oliguria" pattern of the patients with massive cortical necrosis. Hence, the outcome of cortical necrosis will depend considerably upon the amount of tissue involved, and may at times be judged clinically from the pattern of urinary excretion. The evidence in this selected series, however, indicates that patients with extensive renal involvement will not recover.

Histologic examination of available tissues by conventional means offers no more indication of the nature of the pathogenesis of the renal lesion than has been provided from clinical study. Ober and associates [*9*] described nephrosclerosis in the arcuate and interlobar arteries in each of seven cases of renal cortical necrosis following abruptio placentae. However, in the current study renal vascular sclerosis was found in only eleven of twenty-one cases. Thus nephro-

sclerosis does not appear to be a necessary pathologic setting for the development of cortical necrosis. Pre-existing renal disease, however, was present in fifteen of twenty-one cases. (Table IV.) Careful scrutiny of the renal sections in the remaining six cases failed to reveal evidence of underlying abnormality. However, although no specific pathologic renal alterations need be present, their existence may in part be responsible for the development of cortical necrosis.

The evidence for ischemia as the chief pathogenetic factor of cortical necrosis has been summarized by various reviewers [*5,6,8,10*] who cite the primary lesion variously as embolism, thrombosis, vasospasm, vasoparalysis, increased intrarenal pressure, shunting, vascular damage and fibrin deposits. The histologic findings in one patient in the present series clearly demonstrate an embolic etiology, emphasizing the fact that cortical necrosis may be a common end stage of many pathologic processes. This patient (Case 18) had undergone elective resection of an abdominal aortic aneurysm. The surgical procedure was complicated by a rent in the posterior aspect of the aorta at the level of the renal arteries, and repair proved to be difficult. The graft was placed uneventfully otherwise, and the patient was hypotensive only for a short time directly after completion of the procedure. The renal arteries were clearly noted to be pulsating prior to closure of the abdomen. The course, thereafter, was one of renal failure, urinary excretion remaining below 50 cc. per day for the next five days, until death. The gross appearance of the kidneys was characteristic of massive cortical necrosis. However, on microscopic examination numerous cholesterol clefts and atheromatous emboli were identified occluding small vessels of the kidneys, indicating dislodgment from the intima of the aorta. In view of the intensity of this process there seemed little doubt that atheromatous embolization was the major factor in the induction of cortical infarction simulating renal cortical necrosis in distribution. The problem of atheromatous emboli to the kidneys after aortic surgery has been emphasized by Thurlbeck and Castleman [*22*].

Differential Diagnosis. Because the diagnosis of massive cortical necrosis ordinarily connotes a fatal prognosis, the clinical distinction of this lesion from tubular necrosis, which in a majority of instances is reversible, assumes distinct importance.

In our experience the persistence of *total anuria* for one or more days was a common finding in patients with cortical necrosis; in association with tubular necrosis, in contrast, small amounts of urine are usually excreted daily by patients and complete anuria is rare. In a review by Swann and Merrill [*23*] of eighty-five cases of acute renal failure attributed to tubular necrosis there was complete anuria in only one case, an elderly woman with a severe burn of 60 per cent of her body surface. It is possible that cortical necrosis was present in this case since necropsy was not obtained. In every instance of massive cortical necrosis (more than 75 per cent involvement) in our series the degree and duration of oliguria was notable, for there was less than 50 cc. of urine produced for a half or more of the entire course of the disease in each case. Persistent oliguria was especially striking in eight patients in whom the disease lasted more than one week and was unlike the small, incremental increase in daily urinary volume seen during the oliguric phase of tubulorhexic nephrosis. Gjorup et al. [*4*] observed this same phenomenon in their study of cortical necrosis.

Although the urinary sediment is not helpful in differentiating renal cortical necrosis from other causes of renal failure, gross hematuria early in the course of renal failure was noted in six of the fourteen patients in our series in whom accurate records were kept. This observation has been made also by other investigators [*5,8*]. Although gross hematuria does not sharply differentiate renal cortical necrosis from tubular necrosis, it is our impression that it occurs much less frequently in the latter condition.

Abdominal or flank pain was an early and frequent complaint in the present series of patients. It was not possible, however, to determine whether this symptom stemmed from the associated or pre-existing disease or from the renal disorder *per se*. Two of the four patients who had definite renal pain also were noted to have gross hematuria.

Among the twenty-one patients, massive cortical necrosis was strongly suspected in only six on the basis of the clinical course, which was characterized by total anuria or prolonged severe oliguria. These patients were all among those encountered during the latter part of the study when there was an increased awareness of this lesion.

Although there were clinical features that

appeared to be of practical value in differentiating the acute renal failure of massive cortical necrosis from that of tubular necrosis, other renal conditions such as acute glomerulonephritis, acute bilateral renal arterial or venous occlusion, and multiple emboli with extensive renal infarction may also produce an identical clinical picture. The differential diagnosis of the various renal lesions may be impossible, although the over-all clinical course and knowledge of the mode of development of the renal shutdown may provide distinguishing clues.

Percutaneous biopsy of the kidneys during life has been helpful in the differential diagnosis [*5,19,21*]. The biopsy will be of value particularly in excluding massive necrosis if other, more specific disorders such as glomerulonephritis or tubulorhexic nephrosis are recognized in the specimen. It is possible, however, that patchy areas of cortical necrosis may not be sampled by the needle. Furthermore, other lesions of purely necrotic nature, such as isolated or total infarction of the renal parenchyma, may not be differentiated by this means. The final differentiation of cortical necrosis rests upon the pathologic study of the kidney as a whole or of large or appropriately selected segments of the renal tissue.

SUMMARY

Twenty-one cases of bilateral renal cortical necrosis encountered at necropsy over a five-year period are reviewed. Thirteen of these were observed during a seventeen-month period and represented at least 20 per cent of all cases of acute renal failure treated during this interval.

A variety of conditions antedated the renal failure; in only three instances were there preexisting obstetrical complications. Severe renal ischemia is recognized as the most probable common factor accounting for the development of cortical necrosis in these cases.

The clinicopathologic features of the twenty-one cases were analyzed to attempt to differentiate the clinical course of patients with cortical necrosis from those with other causes of acute renal failure. It is apparent that total anuria and severe prolonged oliguria are prominent features of cortical necrosis. Gross hematuria and pain in the flanks also may be important diagnostic clues.

Detailed analysis of these twenty-one cases failed to explain the sudden increase in the incidence of renal cortical necrosis at the Cincinnati General Hospital. It is unlikely that massive cortical necrosis has been overlooked in routine necropsy material. It is conceivable, however, that minor degrees of the process may not have been recognized in the absence of this special interest. No features of therapy were uncovered to explain the heightened incidence, nor were any common epidemiological findings noted in the survey.

ADDENDUM

It is of interest that in the period intervening between the compilation of these data and their preparation for publication the increased incidence has not continued. It is concluded that the large number of cases encountered in such a short period of time must be explained as a chance occurrence.

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Renal Tubular Necrosis Following Lesions of the Brain*

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ACUTE renal failure may complicate a wide range of traumatic and toxic injuries. Yet its occurrence after lesions of the brain has received little attention. In most [*1–5*] clinical studies cerebral damage is not considered a cause of renal failure, although it may be mentioned as an associated injury or illness. In this report five cases will be presented in which brain lesions were followed by acute tubular necrosis, and the significance of this association will be discussed.

Although the morphology and clinical course of acute renal tubular necrosis have been described for more than a century [*6–8*] in association with cholera, trauma and burns, it became an entity only after the World War II, when such etiologic descriptions as "the kidney of crush syndrome" [*9*] and "hemoglobinuric nephrosis" [*1*] were grouped together under "lower nephron nephrosis" [*2*]. Since 1950 this term has gradually become replaced by the anatomically more accurate nomenclature of Bull, "acute tubular necrosis" [*10*].

It has long been known that brain disease may affect renal function. At the turn of the century French neurologists [*11*] described albuminuria occurring in patients with subarachnoid hemorrhage, grand mal epilepsy and brain tumors. Schmidt [*12*] noted transient oliguria in patients with increased intracranial pressure due to brain tumors, and Stucke [*13*] found impaired tubular function in patients who were recovering from cerebral concussions.

Severe renal failure of cerebral origin has been described in only a few case reports. In 1948 Clute and Fitzgerald [*14*] described a case of fatal renal failure following electroshock therapy. Goodman [*15*] reported two similar cases in the same year. In all three cases acute tubular necrosis was found at autopsy. In 1957 Fishberg [*16*] reported a case of neurogenic nephropathy, the clinical course of which was consistent with acute tubular necrosis, following subarachnoid hemorrhage. He explained the nephropathy as a result of renal vasoconstriction.

The hypothesis that acute tubular necrosis can be caused by certain brain lesions is supported by experimental data. It has been well demonstrated that renal ischemia is a major factor in the pathogenesis of acute tubular necrosis. Clearance studies [*10,17–21*] indicate that a variety of injuries—hemorrhage, hemolysis, muscle trauma—lead to marked reduction in renal blood flow. In animals renal vasoconstriction occurring after injuries has been shown by direct visualization of the renal arterial tree with India ink or fluorescent dye [*22,23*], and by direct measurement of renal blood flow [*20*]. Oliver [*23*] studied the effects of injury first with clearance methods and then morphologically with his technic of microdissection of individual nephrons. He found that the necrotic changes are scattered in foci throughout the tubules. Their distribution could only be interpreted on the basis of patchy renal vasoconstriction and ischemia. He concluded that renal ischemia is the final common pathway in the pathogenesis of acute tubular necrosis.

Hoff and associates [*24–26*] showed that renal vasoconstriction may be initiated in the brain. They caused a striking reduction in renal blood flow in cats and monkeys by electrical stimulation of areas in the frontal lobe. The renal vasoconstriction was accompanied by a simultaneous rise in the peripheral arterial blood pressure. Denervation of the kidneys abolished the renal vasoconstriction. In 1951 this group was able not only to produce renal ischemia but also

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the pathological changes characteristic of acute tubular necrosis by repeated electrical stimulation of the anterior sigmoid gyrus in cats [*26*].

The clinical observations of Fishberg, Clute and Goodman, and those herein described, should be viewed in the light of these experiments.

In a series of eighty cases of acute tubular necrosis seen by Kiley [*27*] there were eight in which associated disease or damage of the brain was present. In four the brain disease was the main apparent cause of acute tubular necrosis; in one the cerebral damage was a probable, although not the only etiologic factor; and in three the association was of an incidental nature.

The first five cases form the basis of this report.

CASE REPORTS

Four cases in which brain lesions were the main apparent cause of acute tubular necrosis.

CASE 1. P. E., a forty-seven year old white Brother, was transferred to the Albany Hospital on February 22, 1957, for management of acute renal failure. He had been in excellent health until February 14, 1957, when he retired early because of fatigue. About ten minutes later he was found unconscious on the floor. He was immediately taken to a nearby hospital, where his consciousness returned at the time of admission. Physical examination was non-contributory. The blood pressure was recorded at 140/70 mm. Hg. Laboratory studies included a normal blood urea nitrogen. Examination of the spinal fluid was within normal limits except for a slight elevation of protein.

During the following days it was noted that the patient was oliguric. On the fourth day the urine output was 100 ml. and from the fifth to the seventh day it varied from 200 to 300 ml. The blood urea nitrogen rose gradually, and the patient was transferred to the Albany Hospital for consideration of hemodialysis. Just before arriving he had a seizure.

On admission he was lethargic. Only bits of additional history could be obtained which revealed nothing contributory in the past or family history. Physical examination showed a thin white man who responded to pain but readily slipped back into a semicomatose state. The blood pressure was 200/100 mm. Hg, and the pulse rate 120. The temperature was 100.4°F. The skin was warm and dry; there was no edema. The pupils were small, equal and reactive to light. Examination of the fundi revealed no hemorrhages or exudates, and there was no papilledema. The arteries appeared slightly narrowed. At both bases of the lungs were a few crackling rales. The rest of the physical examination, including the neurological examination, was within normal limits.

The laboratory data were as follows: The urine was acid, had a specific gravity of 1.013, contained a trace of albumin and many red cells. The hemoglobin was 14 gm. per 100 ml., and the hematocrit 46 per cent. The white blood cell count was 8,600 per cu. mm.; the sedimentation rate was 32 mm. in one hour. The serum non-protein nitrogen on admission was 218 mg. per 100 ml. The serum CO_2 combining power was 14, potassium 6.5, sodium 129 and chlorides 92 mEq. per L.

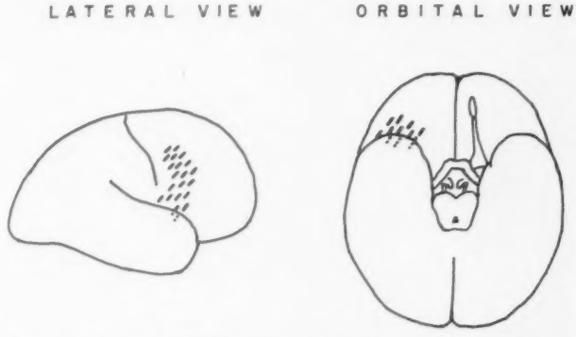


FIG. 1A. Case 1. Diagram of cerebral hemorrhage. Extent at time of autopsy (area of shading).

The next day the patient was less responsive. He exhibited muscle twitching and marked restlessness. He underwent hemodialysis but died suddenly in the afternoon of that day, the ninth of his disease.

Postmortem examination revealed a recent intracerebral and subarachnoid hemorrhage in the right frontal lobe of the brain, acute renal tubular necrosis and moderate hypertrophy of the heart (450 gm.).

There was no evidence of a skull fracture, and the dura mater was intact. The brain was swollen and weighed 1,500 gm. The right frontal lobe was slightly larger than the left. On section there was a zone of hemorrhage close to the surface of the right frontal lobe. (Fig. 1A.) It measured 5 by 3 by 3 cm. and extended into the overlying leptomeninges. The lateral ventricle was compressed but not involved in the hemorrhage. No aneurysm or arteriovenous varix could be demonstrated. The arteries at the base of the brain showed moderate atherosclerosis. Microscopic examination revealed recent hemorrhage with foci of neutrophilic and microglial proliferation. There was cerebral softening in some areas adjacent to the hemorrhage. The kidneys were markedly swollen and pale. The right kidney weighed 260 gm., the left 290 gm. The capsules stripped easily. On microscopic examination the glomeruli were normal. There was slight arteriolar sclerosis. The tubular epithelium showed areas of necrosis with focal regeneration. (Figs. 1B and 1C.) There were pigment casts in the distal and collecting tubules, and there was a moderate interstitial lymphocytic infiltration.

Comment: Acute oliguric renal failure developed in this patient after a hemorrhage in the right frontal lobe, in the absence of any of the

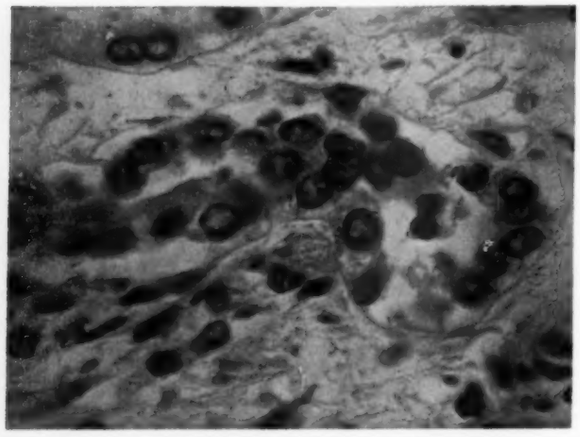


FIG. 1B. Case I. Distal tubule with necrosis and regeneration of epithelium. A few epithelial cells have pyknotic nuclei and are being desquamated. Most cells have giant nuclei and abundant cytoplasm, characteristic of regenerating epithelium.

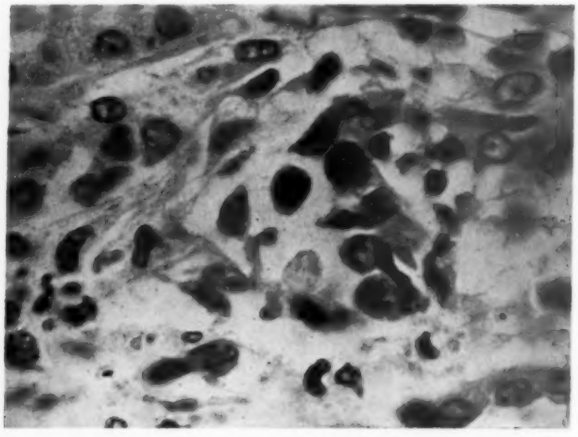


FIG. 1C. Case I. Loss of tubular structure. Large atypical epithelial cells are regenerating in an irregular pattern. Hematoxylin and eosin stain, original magnification × 1,300. Combined weight of the kidneys: 550 gm.

usual initiating causes for acute tubular necrosis. At autopsy there was marked tubular necrosis with evidence of tubular regeneration compatible with the nine-day duration of renal failure. The cardiac hypertrophy and the early arteriolar changes suggested that the patient had had previously asymptomatic hypertensive cardiovascular disease. The extent of the initial hemorrhage was not known. The hemorrhage probably arose in an area of cerebral softening. The patient died from extension of the hemorrhage.

CASE II. K. G., a twenty-one year old white lineman, was transferred to the Albany Hospital on August 29, 1957, with acute renal insufficiency and coma. On August 27 he had sustained a compound fracture of the left femur after a 15 foot fall from a telephone pole. There was no loss of consciousness or memory. He was promptly admitted to a nearby hospital. The blood pressure on admission was 120/80 mm. Hg, and the urine output was described as good on the first hospital day. The next day he became gradually drowsy and twenty-six hours after admission he was in a coma with general hyperreflexia, spasticity of the lower extremities and a bilateral Babinski response. The laboratory results were recorded as follows: The hemogram was normal. The urine was acid, had a specific gravity of 1.023 and contained a trace of albumin; no fat globules were seen. The blood non-protein nitrogen was 22 mg. per 100 ml. Examination of the spinal fluid and the skull roentgenogram was within normal limits.

The temperature rose to 103°F. shortly after the onset of the coma. On the third day the temperature reached 106.2°F. on one occasion. Thereafter it varied around 102°F. The urine output decreased to 535 ml. on the day of hyperpyrexia, then varied from 700 to 1,100 ml. per day. The blood non-protein nitrogen rose gradually to 154 mg. per 100 ml. The blood pressure remained stable. On August 29 the patient was transferred to the Albany Hospital for further management.

Physical examination revealed a comatous, somewhat dehydrated, well nourished white man. The blood pressure was 140/90 mm. Hg, the pulse rate 98 and the rectal temperature 102°F. A few fading petechiae were noted on the conjunctivae and the chest. There was no external evidence of injury to the head. The pupils were equal and reacted to light. The fundi were normal. The eyes moved conjugately on rotation of the head in an opposite direction. There was no stiffness of the neck. Further neurologic examination revealed hyperreflexia and extensor rigidity in all extremities, most marked in the legs. The Hoffmann's finger sign was negative on both sides. The extensor plantar reflexes were positive and equal on both sides. The lower left extremity was encased in a Thomas splint. The rest of the physical examination was within normal limits. Information from the family added nothing of note to the history.

The laboratory studies were as follows: The hemoglobin was 10.4 gm. per 100 ml. and the hematocrit 33 per cent. The white blood cell count was 14,000 per cu. mm. with 80 per cent polymorphonuclear cells, 6 per cent band forms, 7 per cent lymphocytes and 7 per cent monocytes. The platelet count was 522,000 per cu. mm. The urine had a specific gravity of 1.007 and contained 2-plus protein. The sediment revealed a few red cells and an occasional granular cast per low power field. The blood non-protein nitrogen was 184 mg. per 100 ml. and the creatinine 6.5 mg. per 100 ml. The serum sodium was 126, potassium 4.5, CO_2 combining power 14 and chlorides 97 mEq. per

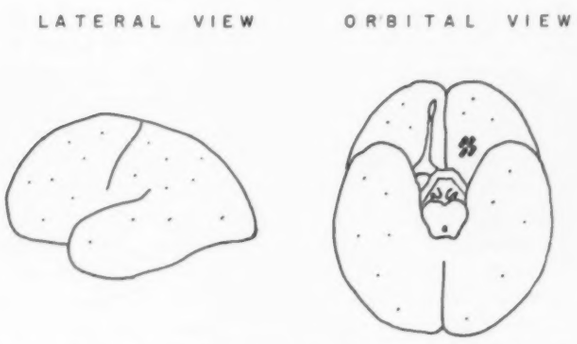


FIG. 2A. Case II. Diagram indicating small focus of hemorrhage in medial orbital gyrus (heavy shading) and multiple small fat emboli in cerebral cortex (stippling).

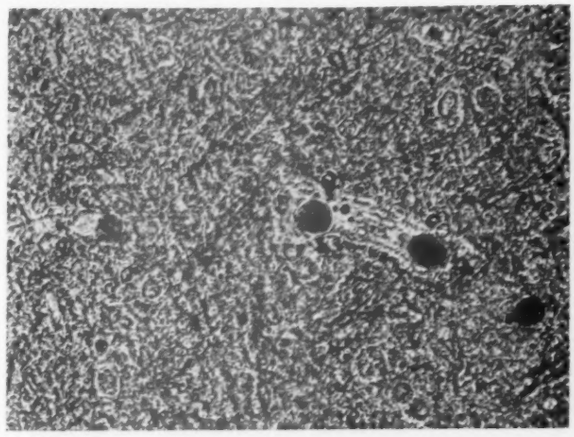


FIG. 2B. Case II. Fat emboli in capillary of cortical grey matter. Sudan IV stain, original magnification × 600.

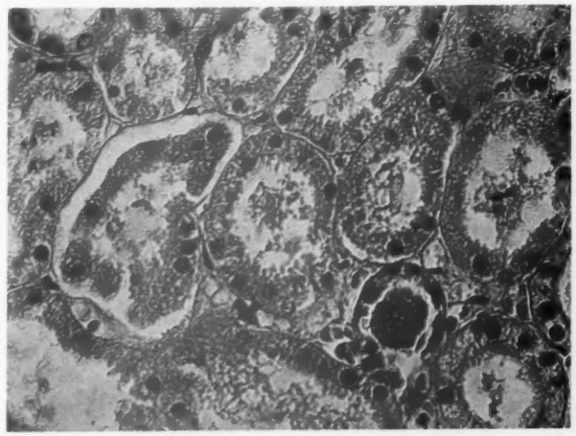


FIG. 2C. Case II. Tubular degeneration and necrosis. Pigment cast in collecting tubule. Hematoxylin and eosin stain, original magnification × 600. Combined weight of kidneys: 570 gm.

L. The Kahn reaction was negative. The bleeding, clotting and prothrombin times were within normal limits. Roentgenograms of the skull, the spine and the chest revealed no abnormalities. The x-ray film of the left femur showed a jagged mid shaft fracture. Lumbar puncture revealed an opening pressure of 190 mm. The fluid was slightly xanthochromic. The total protein content was 36 mg. per 100 ml. There were 6 white and 6 red cells per cu. mm.

It was considered that the patient had a diffuse encephalopathy probably caused by fat embolization. The nature of the renal insufficiency was not clear. There had been no true oliguria and there was a question whether or not the fluid intake had been adequate during the period of coma. Nine hours after admission the patient had a brief generalized convulsion that subsided with the administration of phenobarbital. An attempt to rehydrate failed to increase the urinary output. The blood non-protein nitrogen rose to 268 mg. per 100 ml., and on August 31 he underwent hemodialysis but his coma and neurological signs persisted. The urine output varied around an average of 400 cc. in twenty-four hours. His further course was downhill. An infection of the lower respiratory tract developed and he died on September 6.

The anatomical diagnoses were fracture of the left femur, complete; multiple fat emboli to lungs and brain; bronchopneumonia and congestion of the lungs; acute tubular necrosis, marked, of both kidneys.

There was no evidence of a skull fracture, and the dura mater was intact. The brain appeared moderately swollen and weighed 1,540 gm. There was slight widening of the gyri. Serial sections revealed a small hemorrhagic focus about 5 mm. in diameter in the cortex of the left medial orbital gyrus. (Fig. 2A.) The remainder of the brain appeared normal on gross inspection. On microscopic examination there was moderate edema. Several microscopic foci of fairly recent necrosis were scattered throughout the white matter of the cerebral hemispheres. They contained macrophages, proliferated glial cells and fibroblasts. A single focus of necrosis with pronounced vascularization was observed at the inner margin of the cortical grey matter of the frontal lobe. Fat stains revealed intravascular fat emboli in the areas of necrosis described in the white matter. In addition, fat emboli were found in numerous cortical capillaries without surrounding necrosis. (Fig. 2B.)

The kidneys were grossly swollen. Their combined weight was 570 gm. The capsules stripped with relative ease leaving smooth, pale brown surfaces. On sectioning, both kidneys revealed pale brown, moderately everted and moist cut surfaces. The pyramids were less well defined than usual. On microscopic sections there were many heme casts in the collecting and distal tubules. There were degenerative changes in both the proximal and distal tubules with foci of frank necrosis and disruption of the tubules with irregular regeneration of tubular epithelium. (Fig. 2C.) The glomeruli appeared to be normal. Some of them exhibited widening of the Bowman's space, which contained protein-rich material. The calyces and pelvis were normal.

Comment: This patient's condition was quite satisfactory until fat embolization to the brain and to the lungs occurred. He became comatous and for a brief period hyperpyrexic. Subsequently, his urine output decreased and acute renal failure developed. All recorded blood pressures had been normal. The autopsy revealed multiple fat emboli with small areas of necrosis in the brain and a larger focus of hemorrhage in the left medial orbital gyrus of the frontal lobe. The kidneys contained no fat emboli but exhibited the characteristic changes of acute tubular necrosis.

CASE III. E. H. L., an eighteen year old white truck driver, was brought to the Albany Hospital on July 24, 1950, from the scene of a car accident. He was unconscious but responded to pain stimuli. There was a compound fracture of the skull, and numerous superficial abrasions were present. The injury to the head was the only serious injury. The pulse and blood pressure could not be obtained; the heart rate at the apex was 140. The right pupil was wider than the left one. The muscle strength of the extremities on the left was diminished, and the reflexes on the left were hyperactive with a plantar extensor response. The hemoglobin was 14.5 gm. per 100 ml. The white blood cell count was 39,300 per cu. mm. with 92 per cent segmented forms.

The patient was treated successfully for shock with 1,500 ml. blood, and the blood pressure rose to 110/70 mm. Hg. Shortly after admission a craniotomy was performed. The wound was debrided and the contused brain tissue removed from the right cerebral hemisphere, especially from the posterolateral regions of the frontal lobe.

The patient was anuric on the first day. During the second twenty-four hours his urine output was 290 ml., and the third day 650 ml. His blood non-protein nitrogen gradually rose to 172 mg. per 100 ml. on the sixth day. His urinary output increased to 1,400 on the fifth day and 2,100 on the sixth day. The following week he had an ample diuresis. His blood non-protein nitrogen was still elevated to 112 mg. per 100 ml. on the thirteenth day; thereafter, it gradually returned to normal.

The patient recovered and was discharged on August 12, 1950, with residual paresis on the left side.

Comment: This patient sustained a compound fracture of the skull with laceration of part of the right hemisphere. There were no other injuries of importance. He was hypotensive on admission. After the injury he went through the clinical phases of reversible renal failure, characteristic of acute tubular necrosis.

CASE IV. E. E., a thirty-six year old housewife, received electroshock therapy on July 29, 1953, as treatment for an endogenous depression. When she awoke she complained of nausea and discomfort in the right upper quadrant of the abdomen. The following day it was noted that she had almost no urine output. She was admitted to a nearby hospital for evaluation. The abdominal symptoms subsided but the oliguria persisted. The following record was available: August 4, 45 ml. urine output; August 5, 230 ml. urine output; August 6, 150 ml. urine output. On August 7 she was transferred to the Albany Hospital for management of her renal failure. Past history revealed two other episodes of depression. One had been treated with electroshock therapy without complication. There had been no past or family history of renal disease. There was nothing to suggest the ingestion of poisons.

At the time of transfer the patient appeared friendly, well oriented. She was somewhat overhydrated. The blood pressure was 150/100 mm. Hg, the pulse rate 100. There was a questionable mass in the right upper quadrant. The rest of the physical examination was non-contributory. Laboratory studies on admission revealed a blood non-protein nitrogen of 120 mg. per 100 ml. and a creatinine of 14.1 mg. per 100 ml. The serum potassium was 6.3 mEq. per L., the serum sodium 139 mEq. per L.

The urologist ruled out an obstructive cause for the oliguria. The urine output varied from 200 to 300 ml. from August 8 to August 10. The blood non-protein nitrogen rose to 154 mg. per 100 ml. and the creatinine to 17.7 mg. per 100 ml. On August 10 uremic symptoms became evident from restlessness and poor cerebration. On August 11 hemodialysis was instituted and a good clinical and chemical improvement ensued.

On August 13 the urine output rose to 715 ml. Over the following days, it further increased to values of 3,000 ml. per twenty-four hours. The blood non-protein nitrogen remained around 100 mg. per 100 ml. for two weeks, then gradually returned to normal. The patient was well at a follow-up visit on September 22, 1953.

Comment: This patient became oliguric after electroshock therapy. The subsequent uremia was of such severity that she required hemodialysis. She passed through the typical clinical phases of acute tubular necrosis and made a complete recovery in two months.

A case in which brain damage was a probable although not the only etiologic factor.

CASE V. M. M., a forty-nine year old repair man employed at a cement company, was transferred to the Albany Hospital on February 14, 1958, for management of acute renal failure. For two years he had

had mild asymptomatic hypertension, for which he had not been treated. There had been no history of renal disease.

On February 12 he awoke feeling well and prepared for work in the usual manner. A few minutes later his wife heard a noise in the neighboring room and found him unconscious on the floor. Twenty minutes later he was seen by a physician, who found him in shock with an unobtainable pulse. However, the patient began to respond again and showed no gross neurological abnormalities. It was thought that he had a small cerebral hemorrhage. On admission to a nearby hospital he was oriented, but his blood pressure remained at shock levels around 70/40 mm. Hg. For half a day he received Levophed® and solucortef. Thereafter his blood pressure remained around 170/100 mm. Hg without medication. The patient was catheterized and found anuric on February 12; on February 13 the output remained less than 100 cc. The blood non-protein nitrogen was 44 mg. per 100 ml. on the first day of anuria. On February 14, upon arrival at the Albany Hospital, the patient appeared well oriented. The blood pressure was 180/100 mm. Hg. The pulse rate was 94. The eye grounds revealed grade 2 to 3 hypertensive retinopathy; there was slight weakness of the facial muscles on the left. The rest of the neurological and general examination was within the limits of normal.

The laboratory studies revealed a hematocrit of 38 per cent, a white blood count of 15,000 per cu. mm. The blood non-protein nitrogen was 124 mg. per 100 ml. The electrocardiogram was compatible with left ventricular hypertrophy. The electroencephalogram denoted a focus in the left frontotemporal region as well as diffuse cortical irritability. The cerebrospinal fluid revealed 16 red blood cells per cu. mm. and a protein of 42 mg. per 100 ml.

The patient remained oliguric throughout his stay in the hospital. The blood non-protein nitrogen rose to 212 mg. per 100 ml. On February 18 he became mentally obtunded. The following day he underwent hemodialysis. For a few days he was improved clinically but on February 22 he died suddenly. Permission to perform an autopsy was refused.

Comment: This patient with previously asymptomatic hypertension had a small intracerebral hemorrhage followed by anuria and oliguria. The electroencephalogram denoted a left frontotemporal focus. Unfortunately, postmortem examination was not permitted.

The acute onset of oliguric renal failure after the episode of unconsciousness and the practically normal blood non-protein nitrogen on the first day of anuria are consistent with the clinical diagnosis of acute tubular necrosis. Such a course would be unlikely in malignant nephrosclerosis. In the pathogenesis of the acute tubular necrosis, the cerebral hemorrhage was considered to be an etiologic factor together with the initial hypotension and the administration of norepinephrine, which is known to cause renal vasoconstriction.

COMMENTS

These cases of acute tubular necrosis may be grouped with Fishberg's case [*16*] and with the cases described after electroconvulsive therapy [*14,15*]. They appear to form the clinical counterpart of the experimental tubular necrosis produced in cats by Hoff [*26*]. For the study of cerebral lesions in man, one has to depend on the experiments of nature, which rarely are clearly defined. The lesions in this series could not be localized accurately, yet they occurred predominantly in the frontal lobes, especially in the posterior and orbital regions.

The first patient (Case I) had an extensive intracerebral and subarachnoid hemorrhage in the right frontal lobe. (Fig. 1.) The second patient (Case II) had fat embolization with multiple small foci of necrosis and a larger focus of hemorrhage in the left medial orbital gyrus of the frontal lobe. (Fig. 2.) The third patient (Case III) had a contusion involving the right hemisphere and particularly the posterolateral regions of the frontal lobe. In the fourth patient (Case IV), renal failure followed electroshock therapy and no anatomical data were available. In the fifth patient (Case V) the electroencephalogram indicated a focus over the left frontotemporal region. In Fishberg's patient the renal failure was caused by a subarachnoid hemorrhage [*16*]. He recovered from the renal failure but died ten months later with a large frontal parasagittal tumor (glioblastoma multiforme).

Although these data on the site of brain damage are few, the prevalence of involvement of the posterior regions of the frontal lobe deserves attention, for it is well known that these regions are an important part of the autonomic nervous system. Spencer [*28*] in 1894 studied the influence of electrical stimulation of the orbital surface of the frontal lobe upon respiration; stimulation of certain areas resulted in respiratory arrest and simultaneous changes in the systemic blood pressure. Numerous later investigators [*28–31*] elicited vasomotor responses from the frontal lobes. Fulton [*31*] described the posterior and medial orbital gyri (area 24) and the premotor region as vasomotor areas of the frontal lobe. These regions are closely

TABLE I

SALIENT FEATURES OF ACUTE TUBULAR NECROSIS OF CEREBRAL ORIGIN

Case No., Age (yr.)	Type and Site of Brain Lesions	Associated Disease or Injury	Shock (Prior to oliguria)	Convulsions (Prior to oliguria)	Blood Non-protein Nitrogen (mg. %)	Blood Creatinine (mg. %)	Duration of Oliguria	Outcome	Renal Pathology
Brain Lesions Which Were the Main Apparent Cause of Acute Tubular Necrosis									
I, 47	Area of softening right frontal lobe followed by hemorrhage	Hypertension previously asymptomatic	−	−	235		9	Died	Acute tubular necrosis
II, 21	Fat emboli to brain; hemorrhagic focus in left medial orbital gyrus	Fracture of femur 26 hr. before embolization	−	−	268	13.7	13	Died	Acute tubular necrosis
III, 18	Contusion right cerebral hemisphere—compound skull fracture	Minor abrasions	+	−	172		4	Recovered with residual paresis on left	
IV, 36	Electroshock therapy for endogenous depression	None	−	+	154	15.7	13	Complete recovery	
Brain Lesions a Probable but not the Only Etiologic Factor									
V, 49	Left frontotemporal focus by electroencephalogram; small hemorrhage?	Hypertension previously asymptomatic	+	−	212	17.2	10	Died	No autopsy

related to the "visceral brain" or the limbic system [*32,33*], whereas the anterior parts of the frontal lobe belong to the neocortex, which is phylogenetically younger and concerned with intellectual functions [*34*]. Most of the experiments were carried out in animals. Livingston and associates [*35*] stimulated the orbital surface of the frontal lobe in man, just prior to performing a lobotomy, and elicited a rise in systemic blood pressure. Unfortunately, no data were obtained on the renal blood flow. Pfeiffer and Wolff [*36*] studied renal blood flow in man with clearance methods during periods of stress and emotional strain. They found a decrease in renal blood flow simultaneous with an increase in peripheral arterial blood pressure.

In three of the cases the blood pressure had been normal or elevated; in the other two there had been hypotension. The blood pressure is not a guide for the estimation of renal blood flow. A marked decrease in renal blood flow may occur with normal or high blood pressures as well as in hypotension [*17*]. For example, a normal systemic blood pressure may be maintained at the expense of renal blood flow in "preshock circumstances." On the other hand, a primary disturbance of vasomotor regulation may cause vasoconstriction in the kidneys and in other viscera with a simultaneous elevation of the blood pressure [*25*].

All the patients described here had an acute cerebral insult accompanied by loss of consciousness, and all survived the initial insult by at least a week. Many lesions involving the "visceral brain" doubtless are so rapidly fatal that there is no time for the development of the characteristic tubular changes. Malamud and associates [*37*] demonstrated this time requirement in their study on heat stroke. The incidence of acute tubular necrosis after heat stroke increased with the length of survival. No tubular lesions were noted in rapidly fatal cases. Their study was not only of interest for the time pattern but also for the observations on the pathogenesis of heat stroke. Fluid and salt losses played no role. At autopsy there were degenerative changes in the cerebral cortex, the cerebellum, the basal ganglia and, to a lesser degree, in the hypothalamus.

It would seem likely that renal vasoconstriction occurred as part of a central disturbance of vasomotor and temperature regulation and that the subsequent tubular damage was of cerebral origin.

One patient had had electroconvulsive therapy; the others had had no convulsions prior to the onset of renal failure. Although convulsions may cause an acute acidosis [*15*] and a shift of water [*38*] from the extracellular space into the cells, these changes are transient and unlikely to represent more than secondary factors in the pathogenesis.

Certain cerebral lesions may cause renal

vasoconstriction, which at times—depending on the severity and the duration of renal ischemia—leads to renal tubular necrosis. Little can be said about the mediation of the constrictor effect. In animals it is dependent on an intact nerve supply to the kidney and on the appropriate cortical stimulation. In the clinical material, injury to the brain could either cause a focus of stimulation for constrictor impulses or ablation of an inhibitor region with subsequent release of constrictor activity.

In a number of patients, the lesions appeared to be closely related to the limbic system or the "visceral brain."

More clinical and pathological observations will be needed to localize the areas which govern visceral blood flow in man and to determine the frequency with which lesions of these areas lead to degeneration and necrosis of visceral structures such as the renal tubules.

SUMMARY

Five cases are reported in which brain lesions were followed by acute tubular necrosis. In four of these cases the cerebral damage was the chief apparent cause of renal failure; in one, it was probably of etiologic significance. Although the cerebral lesions could not be localized accurately, they occurred predominantly in the posterior and orbital regions of the frontal lobe, which are closely related to the "visceral brain" or the limbic system.

Experimental data indicate that acute tubular necrosis may be caused by lesions of the brain through a mechanism of renal vasoconstriction.

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Correlation of Lung Macrosections with Pulmonary Function in Emphysema*

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LITTLE has been done to correlate structure and function in pulmonary emphysema. Although numerous advances have been made in the functional appraisal of this disability of the lung, quantitation of the morphologic anomaly has rested upon gross palpation of the lung and random sampling of small fragments of tissue stained by conventional dyes.

The purpose of this investigation was to try to correlate lung function studies obtained during life in thirty-one patients with the degree of emphysema as revealed by whole lung macrosections.

METHOD

The function studies performed consisted of the determination of the vital capacity, total lung capacity, residual volume, maximum breathing capacity, oxygen consumption per liter of air ventilated and alveolar nitrogen percentage after seven minutes of oxygen breathing [*1*].

After death, the trachea and bronchial tree were filled with 10 per cent formaldehyde under a pressure of 20 cm. of water. After fixation, 1 inch-thick slices of lung were imbedded in gelatine and frozen. Whole lung sections, 250μ in thickness were then cut from the thick slices of lung and mounted on paper according to the method of Gough [*2*].

In all cases multiple sections were made from separate parts of one lung. Five to ten sections of each lung were examined. In eleven cases sections were available from both lungs.

To determine the percentage of lung which was emphysematous, a transparent plastic grid, ruled into 1 cm. squares, was used. This grid was placed over the large lung sections on an x-ray view box, and each square centimeter was examined with a hand lens. Each square was graded on a basis of 1 to 10 so that each was given a set of numbers representing the amount of emphysematous, scarred and normal lung (e.g., emphysema 4, scar 1, normal 5). The resultants were added and a single figure for percentage of normal lung, emphysematous lung and scar tissue was obtained. This figure was used for correlation with the various pulmonary function studies.

To ascertain the validity of this method two of the investigators interpreted separately all macrosections. In all but one macrosection, agreement in quantitation was within 8 per cent. The correlation coefficient R for the separate readings was plus 0.89. If serial lung function determinations were available, the last study made before death was selected.

RESULTS

Table I shows the clinical diagnosis, the pulmonary function studies and the estimates of the amount of emphysema present as determined from the macrosections as well as the amount of emphysema as determined during life through a formula applied to certain of the lung function data. This formula will be introduced and discussed subsequently. Table II shows the correlation of the lung function studies and the degree of emphysema as determined from the macrosections. It can be seen from Table II that of all the lung function data, the residual volume percentage of the total lung capacity,

$$\frac{\text{R.V. (Residual Lung Volume expressed in Liters)} \times 100}{\text{T.L.C. (Total Lung Capacity expressed in Liters)}}$$

more nearly expresses the degree of anatomic emphysema present. The larger the percentage of the lung capacity taken up by the residual volume, the greater the degree of anatomic emphysema. The total lung capacity and vital capacity show poor correlation with the amount of anatomic emphysema; in general, the larger the lung volume the greater the emphysema; and the smaller the vital capacity, the greater the degree of anatomic emphysema. The maximum breathing capacity correlates better and in

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TABLE I

CLINICAL DIAGNOSIS CONFIRMED BY POSTMORTEM EXAMINATION AND PULMONARY FUNCTION STUDIES

Case No.	Clinical–Pathological Diagnosis	Vital Capacity		Total Lung Capacity		Residual Volume			Maximum Breathing Capacity		Alveolar N_2 (%)	O_2/L. of Air Ventilated (cc./L.)	Emphysema (%)		
													Macrosection		Lung Function Studies
		L.	% Normal	L.	% Normal	Absolute Values (L.)	% Normal	$\frac{RV}{TLC} \times 100$	L./Minute	% Normal			Right Lung	Left Lung	
27	Emphysema	2.9	78	8.9	175	6.0	225	67	25	26	6.0	20	38	45	65
35	Carcinoma of lung, emphysema	4.1	106	6.6	123	2.5	125	38	106	97	3.4	25	18	33	10
58	Mitral stenosis	3.2	76	4.9	90	1.7	115	38	84	63	2.0	28		6	7
94	Myocardial infarction	4.2	100	7.2	131	3.0	140	42	135	120	1.0	38		13	16
126	Emphysema	2.2	67	6.1	125	3.9	210	64	27	32	4.7	28	45	40	43
138	Bronchiolectasia	1.8	47	5.1	98	3.3	220	65	63	48	14.2	18	49		34
148	Silicosis, emphysema	1.7	44	3.2	64	1.5	155	48	22	21	1.8	29	22		27
149	Emphysema	2.2	59	6.9	130	4.7	225	69	30	30	7.6	38	48	53	50
150	Emphysema	2.0	60	5.3	104	3.3	205	62	33	38	3.7	17	37	45	33
160	Lung abscess, emphysema	3.3	74	5.9	103	2.6	145	46	53	47	2.0	25		18	16
163	Emphysema	2.5	76	5.2	106	2.7	170	52	38	45	7.0		30	39	23
165	Aortic stenosis	3.9	111	6.5	128	2.7	142	41	62	63	2.0	29	32	32	14
166	Emphysema	1.5	41	6.0	119	4.5	250	75	15	17	5.8	24	67	70	54
169	Rheumatic heart disease	3.0	81	4.5	88	1.5	105	33	103	106	1.7	26	6	6	3
178	Carcinoma of lung, emphysema	2.0	63	3.6	75	1.6	145	44	47	60	1.8	38	16	12	11
179	Hodgkin's disease	0.9	30	1.8	49	0.9	165	50	22	30	1.2	31		4	10
180	Emphysema	1.5	38	3.7	69	2.4	220	60	13	11	1.4	32	32		21
181	Pulmonary fibrosis (Hamman-Rich)	1.3	49	2.9	79	1.6	185	54	62	83	2.2	28		15	19
182	Pulmonary tuberculosis	1.1	28	2.4	46	1.3	180	54	53	49	2.4	64	14		11
183	Bronchiolectasia	1.9	42	6.0	109	4.1	230	68	35	32	18.5			60	41
185	Broncho-pneumonia	3.0	90	5.7	114	2.7	155	48	72	83	3.5	28	9		20
201	Rheumatic heart disease	2.7	85	4.0	100	1.3	110	34	59	61	3.6	45	9		4
207	Aortic aneurysm, emphysema	2.6	75	6.7	136	4.1	205	61	38	40	3.7	37	17	21	42
215	Pneumoconiosis, emphysema	1.8	53	5.2	106	3.4	215	66	14	19	5.0	51	56		38
223	Emphysema	1.1	30	6.8	127	5.7	285	84	22	21	5.0	38	75		69
228	Lymphoma, emphysema	3.7	100	6.5	125	2.8	140	43	119	120	1.7	23		18	16
237	Emphysema	1.8	72	5.2	139	3.4	220	65	26	39	1.8	19	37		49
238	Carcinoma of colon, emphysema	2.2	60	7.4	136	5.2	235	70	138	44	2.2	28	49		55
273	Lymphatic leukemia, emphysema	2.5	84	4.5	93	2.0	135	45	88	130	4.6	30	22		14
274	Carcinoma of stomach, emphysema	3.1	92	7.0	137	3.8	180	55	56	75	1.6	23		39	34
279	Rheumatic heart disease	4.8	114	7.7	138	2.9	125	38	121	105	0.8	25	8		12

NOTE: The last two columns show the degree of emphysema as determined from the macrosection, and the degree of emphysema as determined through a formula applied to certain of the lung function data. This formula is discussed in the text. The predicted values used for the lung functions are those of Baldwin et al. [7].

TABLE II

CORRELATION BETWEEN THE AMOUNT OF EMPHYSEMA AS SCANNED ON THE MACROSECTIONS AND EACH ONE OF THE LUNG FUNCTION STUDIES MENTIONED IN THE FIRST COLUMN

Lung Function	Correlation Coefficient*
$\frac{\text{Residual volume (L.)}}{\text{Total lung capacity}} \times 100$	+0.75
Residual volume per cent normal	+0.80
Total lung capacity (TLC)	+0.41
Vital capacity	−0.41
Maximum breathing capacity	−0.62
Alveolar nitrogen after 7 minute O_2 breathing	+0.52
Oxygen consumption:L. ventilated	−0.04
$\left[\left(\frac{RV}{TLC} \times 100\right) - 30\right] \times \frac{TLC}{\text{Predicted TLC}}$	+0.80

* The correlation coefficient is calculated according to the method of Hill [4]. This expresses the results in terms of plus 1 to minus 1, plus 1 being perfect positive correlation and minus 1 perfect negative correlation. Zero indicates no correlation at all.

a negative direction; i.e., the greater the emphysema, the smaller the maximum breathing capacity. The percentage of alveolar nitrogen shows fair correlation; the greater the alveolar nitrogen after seven minutes of oxygen breathing, the greater the degree of emphysema. Oxygen consumption per liter ventilated showed no correlation at all with the degree of emphysema.

COMMENTS

In order to detect emphysema in asymptomatic persons and in those with only a slight alteration of function, an attempt was made to formulate a quantitative expression of the amount of emphysema present during life based on the lung function studies. The favorable correlation of the ratio of the residual volume:total lung capacity suggested that this determination might be useful for this purpose.

As the absolute value of the residual volume may not always fall below normal when the total lung capacity is decreased, ratios of high residual volume:total lung capacity may be obtained. If the total lung capacity is greater than the predicted normal, the amount of emphysema may be even greater than implied by the increase in the ratio of residual volume:

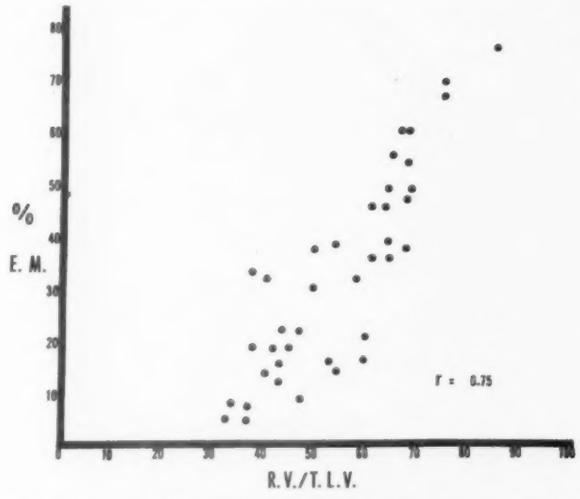


FIG. 1. Correlation between the residual volume per cent of the total lung capacity and the amount of emphysema as estimated from the macrosection.

total lung capacity. Also Figure 1 seems to indicate that if this ratio is less than 30 macroscopic emphysema is not present. On the basis of these considerations, a formula for estimating the amount of emphysema present during life was obtained by subtracting 30 from the ratio of residual volume:total lung capacity and multiplying the resultant figure by the observed total lung capacity divided by the predicted value:

$$[(RV/TLC \times 100) - 30] \times \frac{TLC}{\text{Predicted TLC}}.$$

The correlation coefficient R between the figures obtained and the per cent of anatomic emphysema obtained by macrosection was plus 0.8.

The errors inherent in the determination of pulmonary function are well recognized. Correlations between these tests, x-ray studies and clinical disability of emphysematous persons have been thoroughly investigated [3], but the quantitative relationship between the degree of anatomic anomaly and the decrease in function has not been as thoroughly delineated. Macrosections of the lung offer a reliable means of quantitating anatomically the degree of emphysema present at death. Such sections contribute a valuable appraisal of pulmonary function technics obtained during life.

Figures 2, 3, 4 and 5 illustrate the correlation of emphysema determined by pulmonary function and by pathologic estimate in four cases. It is apparent from these macrosections that the degree of emphysema differs markedly, and the



FIG. 2. Macrosection illustrating small areas of emphysema in the apex. Antemortem estimate 3 per cent emphysema; postmortem estimate 6 per cent.

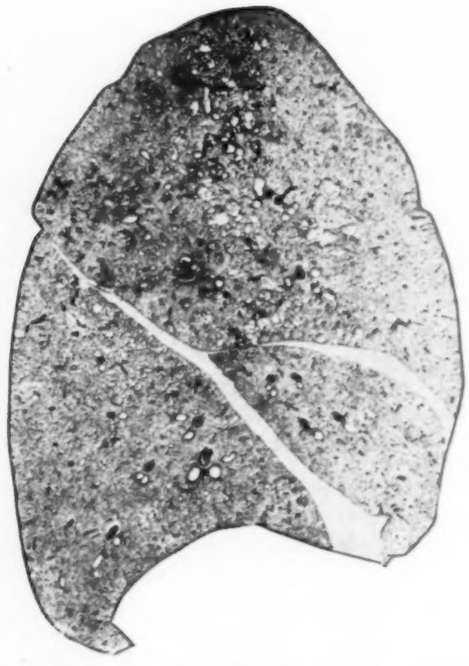


FIG. 3. More extensive emphysematous change than is shown in Figure 2. Multiple areas of emphysema are seen in the upper lobe and in the upper portion of the lower lobe of the right lung. Antemortem estimate 14 per cent emphysema; postmortem estimate 22 per cent.



FIG. 4. Well established emphysema with localized areas of lung destruction. Antemortem estimate 42 per cent emphysema; postmortem estimate 45 per cent.



FIG. 5. Extensive emphysema with only small islands of normal lung remaining. Antemortem estimate 69 per cent emphysema; postmortem estimate 75 per cent.

antemortem estimate closely parallels the postmortem evaluation.

Almost all the lungs examined showed some degree of emphysematous change, although this was not always the major diagnosis. Table 1 illustrates that there were nine cases (Cases 27, 126, 149, 150, 163, 166, 180, 223, 237) in which emphysema was the principal diagnosis. In all these cases at least 30 per cent of the lungs were emphysematous. It is difficult to estimate the degree of emphysema that must be present before the disease manifests itself symptomatically by shortness of breath; but from the analysis of

these cases it appears that 15 to 20 per cent of the lung must be involved before emphysema produces significant dyspnea on exertion.

The formula suggested gives an estimate of the degree of emphysema present during life and correlates well with the degree found at postmortem examination. This formula should help in making a diagnosis in patients with only slight involvement in whom clinical signs or symptoms are not marked or are absent, and it should be of assistance in following the progression of the disease. From the study of such cases, a better understanding of the natural history and treatment of this disease may evolve.

SUMMARY AND CONCLUSION

1. Macrolung sections have been used to estimate the degree of emphysema present at death and this estimation has been compared with pulmonary studies.

2. The ratio of residual volume:total lung capacity shows the best correlation with the degree of emphysema; the maximum breathing capacity and alveolar nitrogen after seven minutes of oxygen breathing do not correlate as well with the degree of emphysema. The total lung capacity and vital capacity show poor correlation, while oxygen consumption per liter ventilated exhibits none.

3. A method of quantitating the amount of emphysema during life is proposed. The proposed formula reflects the degree of anatomic destruction present, and should aid in the study of the evolution of emphysema.

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Metabolic and Radioactive Tracer Studies in Carcinoma of the Prostate*

Effect of Diethylstilbestrol and of Orchiectomy

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THE modalities of treatment of metastatic carcinoma of the prostate and the beneficial effects of female hormones in the palliative therapy of this disease have been well established [*1–7*]. The metastatic process of this tumor when it involves the skeleton differs from that of other tumors in its predominantly osteoblastic reaction. The roentgenographic evidence of diffuse osteoblastic metastases in conjunction with elevation of the plasma acid phosphatase [*8–10*] in a male patient is virtually diagnostic of this tumor.

A detailed metabolic study carried out on a patient with carcinoma of the prostate before and during treatment with diethylstilbestrol was reported from this institution several years ago [*11*]. It was found that the calcium balance of this patient was normal despite the fact that he was in an active phase of metastatic bone disease and was maintained on a low calcium intake. Metabolically, the administration of estrogen led to marked retention of calcium. In an attempt to investigate further the derangements of calcium metabolism caused by this tumor a larger number of patients with carcinoma of the prostate metastatic to bone were studied by means of metabolic balances, the calcium tolerance test and radioisotope technics. These studies are reported in this communication. Some of the results obtained were previously presented [*12*].

MATERIALS AND METHODS

Seventeen patients with carcinoma of the prostate were investigated under controlled dietary conditions on the Metabolic Research Ward. The type and duration of the studies performed are listed in Table 1. The age of the patients ranged from fifty-eight to eighty-one years. The diagnosis was proved histologically in fifteen patients; the remaining two patients had clinical and laboratory evidence of prostatic carcinoma, namely, a hard, nodular prostate, elevation of the serum acid phosphatase and osteoblastic bone lesions. All patients with the exception of one (Case 10) had roentgenographic evidence of metabolic bone disease and all but one with bone metastases (Case 7) had severe bone pain. In eight of these patients (Cases 8 through 14 and Case 16) orchiectomy was performed at varying time intervals prior to the start of the study; these patients had derived palliative benefit from this procedure in the past and had exacerbation of the disease at the time of study.

Metabolic balance studies of calcium, nitrogen and phosphorus were performed in thirteen patients. The balance studies in two patients (Cases 1 and 13) were measured in the control phase only, whereas in eleven patients they were studied in the control and treatment phase. The duration of the metabolic studies ranged from thirty-one to 238 days and averaged 107 days. In the treatment phase 15 mg. of diethylstilbestrol were given intramuscularly per day. In most patients the metabolic effect of diethylstilbestrol was studied immediately following the control period; the effect of prolonged administration of this hormone was investigated in three metabolic balance studies in one patient (Case 2). A summary of the earlier metabolic observations made on this patient [*11*] is included in this communication for comparison, since a twelve-day metabolic study was performed after two years of continuous diethylstilbestrol administration. Two patients were studied before and after orchiectomy (Cases 6 and 7).

Calcium tolerance tests [*13–15*] were performed in fifteen patients, in eight both before and during stilbestrol therapy. Two patients were tested after they had received female hormone for varying periods of time (Cases 2 and 6). In this test, 50 ml. of 10 per

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† Deceased June 1, 1958.

TABLE I
LIST OF PATIENTS STUDIED

Case No.	Age (yr.)	Treatment	Skeletal Involvement	Studies Performed	Duration of Studies (days)
1	81	None	Diffuse osteoblastic	Metabolic balances, calcium tolerance test, $Sr^{85} + Ca^{45}$ orally	36
2	70	Stilbestrol	Extensive osteoblastic	Metabolic balances, calcium tolerance test	105
3	60	Stilbestrol	Extensive osteoblastic	Metabolic balances	238
4	70	Stilbestrol	Osteoblastic	Metabolic balances, calcium tolerance tests	31
5	59	Stilbestrol, calcium gluconate	Osteoblastic	Metabolic balances, calcium tolerance tests, $Ca^{45} + Sr^{85}$ oral, Sr^{85} intravenously	184
6	68	Orchiectomy, stilbestrol	Osteolytic and osteoblastic	Metabolic balances, calcium tolerance tests	222
7	67	Orchiectomy, stilbestrol, calcium gluconate	Extensive osteoblastic	Metabolic balances, calcium tolerance tests	48
8	65	Stilbestrol*	Predominantly osteoblastic	Metabolic balances	61
9	68	Stilbestrol*	Extensive osteoblastic and osteolytic	Metabolic balances, calcium tolerance tests, Ca^{45} intravenously	51
10	76	Stilbestrol,* calcium gluconate	No metastases, osteoporosis	Metabolic balances, calcium tolerance tests, Ca^{45} intravenously	138
11	64	Stilbestrol*	Osteoblastic	Metabolic balances, calcium tolerance tests	55
12	75	Stilbestrol*	Predominantly osteoblastic	Metabolic balances, calcium tolerance tests, Ca^{45} intravenously	169
13	74	None*	Predominantly osteoblastic	Metabolic balances, calcium tolerance tests, Sr^{85} intravenously	58
14	59	Stilbestrol*	Extensive osteoblastic	Calcium tolerance test, Ca^{45} intravenously	21
15	79	None	Osteoblastic	Calcium tolerance test	3
16	58	Stilbestrol*	Osteolytic and osteoblastic	Calcium tolerance tests	30
17	73	Stilbestrol	Predominantly osteoblastic	Calcium tolerance tests	27

NOTE: Diethylstilbestrol, 15 mg./day, was given intramuscularly.
* Orchiectomy performed at varying time intervals prior to the studies.

cent calcium gluconate (containing 469 mg. Ca^{++}) are infused in 500 ml. 5 per cent glucose in water over a 4-hour period in the fasting state. The twenty-four hour urinary excretion of calcium on the day before the test, the day of the test and the day thereafter is determined and the amount of the infused calcium retained is calculated. The serum calcium and phosphorus levels are determined before the calcium infusion, immediately after its termination, and twenty hours thereafter. In order to study the early effects of diethylstilbestrol on urinary excretion of calcium and on calcium retention, calcium tolerance tests were performed in four patients during the control phase and in short succession following the institution of treatment (Cases 4, 11, 16 and 17).

Radiocalcium studies were carried out in six and radiostrontium studies in three patients, respectively. Ca^{45}, a β-emitter with a half life of 152 days and Sr^{85}, a γ-emitter with a half life of sixty-five days, were used as tracers. Four patients received a single tracer dose of Ca^{45} (0.5 μc./kg. body weight) as the chloride, intravenously, in the postabsorptive state (Cases 9, 10, 12 and 14). The plasma levels, urinary and fecal excretions of Ca^{45} were followed for as long as ninety-

TABLE II

MINERAL AND PROTEIN METABOLISM OF PATIENTS WITH CARCINOMA OF THE PROSTATE AND EFFECT OF DIETHYLSTILBESTROL

Case No.	Study (days)	Treatment	Calcium (mg./day)				Phosphorus (mg./day)				Nitrogen (mg./day)			
			Intake	Urine	Stool	Balance	Intake	Urine	Stool	Balance	Intake	Urine	Stool	Balance
1	18	None	134	16	224	−106	680	568	183	− 71	10700	10045	623	+ 32
2	24	None	162	95	227	−160	513	278	240	− 4	8480	8208	928	− 656
	42	Stilbestrol	169	27	167	− 25	550	259	241	+ 50	8823	8372	1019	− 568
	24*	Stilbestrol	142	14	89	+ 39	563	283	217	+ 53	9168	8583	825	− 240
	12†	Stilbestrol	132	37	123	− 28	615	498	196	− 79	8502	9420	435	−1353
3	54	None	149	20	181	− 52	530	201	229	+100	9135	7108	1179	+ 846
	44	Stilbestrol	156	14	158	− 16	648	218	230	+200	8593	7188	1180	+ 225
4	6	None	112	57	121	− 66	400	521	178	−299	6106	9191	808	−3893
	12	Stilbestrol	151	18	124	+ 9	588	369	166	+ 53	9417	7787	778	+ 852
5	36	None	942	110	765	+ 67	678	478	233	− 33	10931	9362	1062	+ 507
	48	Stilbestrol	953	44	723	+186	730	397	293	+ 60	12014	10833	1004	+ 177

* Study was started after ninety days of diethylstilbestrol administration.
† Study performed after two years of diethylstilbestrol treatment.

eight days. Two Ca^{45} studies were carried out in one patient (Case 12): one during the control phase and one after sixty-eight days of diethylstilbestrol administration. The duration of this second tracer study was forty-two days. Two patients (Cases 1 and 5) received a tracer dose of Sr^{85} and Ca^{45} orally. The duration of these studies was twenty-eight and 102 days, respectively. The urinary excretion of calcium and phosphorus was determined daily during the entire duration of all Ca^{45} and Sr^{85} studies. Each stool specimen was separately radioassayed. Sr^{85} was counted in a well-type scintillation counter, Ca^{45} in a Q-gas flow counter following precipitation of calcium as the oxalate. The technics of the administration of the tracers and of the radioassay of Sr^{85} and Ca^{45} were previously published [*15–19*].

All patients received a constant, analyzed, low calcium diet for the entire duration of the study [*20*]. The diet contained 1,850 calories (68 gm. protein, 265 gm. carbohydrate and 59 gm. fat); the daily intake of dietary calcium and phosphorus averaged approximately 150 and 700 mg., respectively. The fluid intake was kept constant. The effect of calcium added to the diet in the form of calcium gluconate tablets was studied in three patients (Cases 5, 7 and 10). All other constituents of the diet were kept constant. The utilization of the added calcium was calculated according to the formula of Steggerda and Mitchell [*21*].

The excreta (urine and stool) were analyzed for nitrogen, calcium and phosphorus in aliquots of each six-day metabolic pool. Analyses of nitrogen were performed by the Kjeldahl method, of phosphorus by the method of Fiske and SubbaRow [*22*], urinary calcium by the method of Shohl and Pedley [*23*]. Stool calcium and phosphorus were determined in ashed aliquots of six-day metabolic pools. The diet was analyzed for the same constituents as the excreta. In addition, determinations of sodium and potassium of the diet were made by flame photometer.

METABOLIC STUDIES

Table II shows data of the metabolic balances of nitrogen, calcium and phosphorus of five patients with carcinoma of the prostate in the control phase and of four of these during the administration of diethylstilbestrol. In the control phase the urinary excretion of calcium was within the normal range in three patients with osteoblastic metastases (Cases 2, 4 and 5) and was extremely low in two others (Cases 1 and 3). The calcium balances ranged from +67 to −160 mg./day. The major metabolic effect of diethylstilbestrol therapy was a decrease of the urinary excretion of calcium, except in one patient (Case 3) who had low calciuria prior to treatment. The fecal excretion of calcium remained unchanged in three patients during

the treatment phase and decreased in one during prolonged administration of diethylstilbestrol (Case 2). The calcium balance study performed in this latter patient after two years of continuous stilbestrol intake gave results similar to that performed immediately following the control phase, −28 and −25 mg./day, respectively. Concomitant with the decrease in urinary excretion of calcium the calcium balances of the treated patients became more positive (or less negative). The phosphorus balances followed the trend of the calcium balances. Diethylstilbestrol had no consistent effect on the nitrogen balance: it became slightly less positive in two patients and improved in two others.

The effect of orchiectomy and of subsequent administration of diethylstilbestrol on urinary excretion of calcium is illustrated in Figure 1. Prior to orchiectomy the urinary excretion of calcium of one patient (Case 6), determined for nine six-day periods, averaged 152 mg./day. In the sixty-six days following this procedure the calciuria decreased to approximately half of the control excretion and a further marked decrease occurred during diethylstilbestrol administration. The patient then failed to continue with stilbesterol medication. Sixteen weeks after discontinuation of hormone therapy the urinary excretion of calcium had markedly increased and exceeded the control excretion.

Data on the effect of orchiectomy on the nitrogen and mineral metabolism of two patients are shown in Table III. Prior to orchiectomy the urinary excretion of calcium of one patient (Case 6) was relatively high, 186 mg./day, that of another (Case 7) in the low normal range, 56 mg./day. Following this procedure the calciuria of the former decreased while that of the latter remained unchanged. No appreciable decrease of fecal excretion of calcium was noted. Both patients had marked nitrogen retention following orchiectomy. The nitrogen balance of the

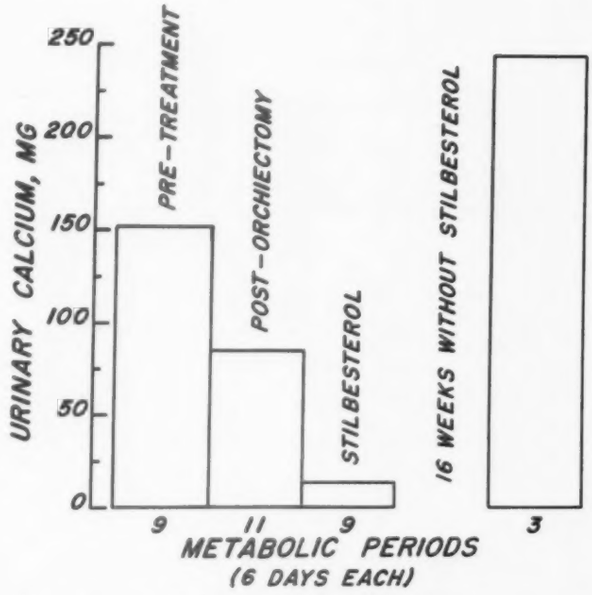


FIG. 1. Case 6. Effect of orchiectomy on urinary excretion of calcium.

two patients improved by 4.5 and 2.1 gm./day, respectively.

Table IV shows the metabolic balances of seven patients in whom orchiectomy had been performed at varying time intervals prior to the study. In six of these the effect of diethylstilbestrol therapy was also studied. The urinary excretion of calcium ranged from low to normal values in four patients (Cases 6, 10, 12 and 13), was low in two (Cases 8 and 9) and higher than normal in one (Case 11). The calcium balances of six of these patients were slightly negative, as in normal subjects during low calcium intake; the balance of the seventh patient (Case 11) was distinctly negative, −360 mg./day. With the institution of diethylstilbestrol therapy the calciuria decreased in the patients with urinary excretions of calcium in the normal range or higher, whereas there was no further change in the calciuria of those who had subnormal excre-

TABLE III

EFFECT OF ORCHIECTOMY ON CALCIUM, PHOSPHORUS AND NITROGEN METABOLISM

Case No.	Study (days)	Treatment	Calcium (mg./day)				Phosphorus (mg./day)				Nitrogen (mg./day)				Serum (mg. %)	
			Intake	Urine	Stool	Balance	Intake	Urine	Stool	Balance	Intake	Urine	Stool	Balance	Calcium	Phosphorus
6	15	None	176	186	298	−308	544	357	276	− 89	8345	8417	1291	−1363	10.3	4.5
	69	Orchiectomy	197	96	239	−138	663	318	218	+127	9820	5455	1230	+3135	9.4	3.9
7	18	None	569	56	414	+ 99	629	397	323	− 91	9400	8652	975	− 227	10.2	3.5
	21	Orchiectomy	614	74	373	+167	616	333	227	+ 56	9853	6894	1052	+1907	10.2	3.2

TABLE IV

EFFECT OF DIETHYLSTILBESTROL THERAPY ON MINERAL AND PROTEIN METABOLISM OF PREVIOUSLY ORCHIECTOMIZED PATIENTS

Case No.	Study (days)	Treatment	Calcium (mg./day)				Phosphorus (mg./day)				Nitrogen (mg./day)			
			Intake	Urine	Stool	Balance	Intake	Urine	Stool	Balance	Intake	Urine	Stool	Balance
6	69	None	197	96	239	−138	663	318	218	+127	9820	4547	1230	+4043
	24	Stilbestrol	190	22	192	− 24	600	266	185	+149	10111	7238	1258	+1615
8	18	None	109	12	258	−161	214	58	212	− 56	4475	4933	711	−1169
	18	Stilbestrol	102	10	111	− 19	183	45	117	+ 21	3453	4944	427	−1918
9	18	None	152	29	229	−106	620	252	227	+114	8990	6915	611	+1464
	6	Stilbestrol	128	29	275	−176	622	132	173	+317	8879	7526	1331	+ 22
10	24	None	177	80	165	− 68	621	424	162	+ 35	8687	7078	914	+ 695
	36	Stilbestrol	186	44	154	− 12	594	304	149	+141	9295	7343	933	+1019
11	12	None	185	322	223	−360	862	709	285	−132	13783		1061	
	24	Stilbestrol	144	85	261	−202	556	406	268	−118	8054		993	
12	12	None	137	57	229	−149	691	289	285	+117	11544	8753	1787	+1004
	48	Stilbestrol	117	29	218	−130	592	282	294	+ 16	10188	7387	1743	+1058
13	42	None	112	49	98	− 35	568	304	165	+ 99	8840	7369	589	+ 882

NOTE: Orchiectomy was performed several months prior to the studies.

tion of calcium before hormone therapy was instituted. The fecal excretion of calcium remained in the same range in five patients during hormone administration and decreased in only one patient (Case 8). The calcium balances became less negative in four patients (Cases 6, 8, 10 and 11), remained unchanged in one (Case 12), and became slightly more negative in one other (Case 9) due to a somewhat decreased calcium intake and a slight increase in fecal excretion of calcium in the treatment phase. No consistent effect of diethylstilbestrol therapy on the nitrogen and phosphorus balances was noted. The nitrogen balances became less positive in three patients, remained unchanged in one, and improved in one other.

Table v shows the metabolic effect of adding calcium gluconate to the low calcium diet. No increase in urinary excretion of calcium was observed during the period of calcium supplementation. The fecal excretion of calcium increased in each of the three patients, the calcium balances improved in two and remained unchanged in the third patient (Case 10). The urinary excretion of phosphorus changed slightly in either direction. The fecal excretion of phosphorus tended to be higher in the calcium gluconate phase. The utilization of added calcium was 22 and 39 per cent in two patients (Cases 5 and 7, respectively). The calcium balance of one patient (Case 10) failed to improve; the added calcium was not utilized.

CALCIUM TOLERANCE TESTS

Table VI shows the results obtained with the calcium tolerance tests. The urinary excretion of calcium of the untreated patients (in whom no previous orchiectomy was performed) ranged from low to normal levels (Cases 1, 15, 5 and 7). The retention of infused calcium was in the normal range in two (Cases 7 and 15), considerably higher than normal in one (Case 1), and in the low normal range, 49 per cent, in another (Case 5). (The calcium retention of persons with normal bone metabolism [*14,15*] averages 71 per cent.) Similarly, the urinary excretion of calcium of four patients in whom orchiectomy previously had been performed (Cases 9, 10, 13 and 14) was either in the normal range or extremely low (Case 13). The calcium retention

TABLE V

METABOLIC EFFECTS OF CALCIUM ADDED TO THE LOW CALCIUM DIET

Case No.	Study (days)	Treatment	Calcium (mg./day)				Phosphorus (mg./day)				Calcium Supplementation, Difference in		Utilization* (%)
			Intake	Urine	Stool	Balance	Intake	Urine	Stool	Balance	Intake (mg./day)	Balance (mg./day)	
5	34	None	168	124	150	−106	676	559	194	− 77	...	...	...
	36	Calcium gluconate	942	110	765	+ 67	678	478	233	− 33	786	+173	22
7	6	None	135	65	139	− 69	579	310	178	+ 91	...	...	...
	18	Calcium gluconate	569	56	414	+ 99	629	397	323	− 91	434	+168	39
10	36	Stilbestrol*	186	44	154	− 12	594	304	149	+141	...	...	...
	36	Stilbestrol* and calcium gluconate	604	44	589	− 29	650	278	238	+134	418	Not improved	...

* Utilization = $\frac{\text{Improvement in balance}}{\text{Increment in intake}} \times 100$.

† 15 mg./day.

TABLE VI

CALCIUM TOLERANCE TESTS PERFORMED IN PATIENTS WITH CARCINOMA OF THE PROSTATE BEFORE AND DURING THE ADMINISTRATION OF DIETHYLSTILBESTROL

Case No.	Treatment	Serum (mg. %)		Urinary Calcium (mg./day)			Urinary Phosphorus (mg./day)			Calcium Retention* (%)
		Calcium	Phosphorus	Pre Day	Test Day	Post Day	Pre Day	Test Day	Post Day	
1	None	10.0	3.0	17	17	14	573	403	408	97
10	None†	10.5	3.4	102	256	121	...	206	450	65
13	None†	10.7	3.0	10	35	7	284	190	169	95
14	None†	10.4	2.5	68	216	85	296	159	388	67
15	None	11.0	3.8	139	302	202	487	385	318	76
	None	10.7	3.4	99	338	106	497	454	579	49
5	Diethylstilbestrol 44 days	9.8	2.8	27	185	21	385	295	361	66
	105 days	10.0	2.7	26	183	36	656	580	752	67
7	None	9.9	3.2	63	251	91	323	389	400	58
	Diethylstilbestrol† 240 days	8.6	4.1	6	23	9	365	351	381	96
9	None†	9.1	3.4	43	75	50	211	173	261	93
	Diethylstilbestrol 18 days	8.0	2.7	13	80	15	239	250	226	85
12	None†	9.7	3.8	83	193	91	339	209	248	75
	Diethylstilbestrol 60 days	9.5	2.6	20	70	19	316	175	294	89
2	Diethylstilbestrol 2 years	10.4	3.0	39	223	54	542	392	422	59
6	Diethylstilbestrol† 27 days	9.1	3.2	30	65	14	282	258	218	92

NOTE: Diethylstilbestrol, 15 mg./day, was given intramuscularly.

* Expressed in per cent of infused calcium (469 mg.).

† Orchiectomy performed several months prior to this study.

TABLE VII

SERIAL CALCIUM TOLERANCE TESTS PERFORMED TO STUDY THE EFFECT OF DIETHYLSTILBESTROL THERAPY

Case No.	Treatment	Serum (mg. %)		Urinary Calcium (mg./day)			Urinary Phosphorus (mg./day)			Calcium Retention* (%)
		Calcium	Phosphorus	Pre Day	Test Day	Post Day	Pre Day	Test Day	Post Day	
4	None									
	Test 1	10.8	3.8	57	89	98	473	370	411	93,84†
	Test 2	10.9	3.5	51	111	31	363	315	558	87
	Diethylstilbestrol									
	3 days	9.9	3.5	12	41	14	317	371	431	94
	6 days	9.5	3.0	14	40	17	366	315	345	94
	9 days	10.5	3.1	13	49	17	355	296	393	92
	13 days	9.6	2.8	26	48	29	470	351	506	95
	17 days	9.2	2.8	28	53	25	502	407	434	95
11‡	None									
	Test 1]	11.2	4.9	304	482	311	743	680	598	62
	Test 2	12.4	4.7	277	466	296	624	600	648	60
	Diethylstilbestrol									
	3 days	11.3	4.1	187	323	124	593	335	372	71
	6 days	10.3	3.7	118	308	93	397	404	466	59
	9 days	11.2	3.7	73	258	69	465	458	461	61
	16 days	10.3	3.0	72	236	44	347	129	344	65
	22 days	10.2	3.2	32	178	25	312	176	369	69
16‡	None									
	Test 1	9.1	4.0	57	160	80	500	331	504	77
	Test 2	9.6	3.8	82	150	85	438	232	277	85
	Diethylstilbestrol									
	8 days	8.7	3.4	35	39	24	338	300	420	99
	17 days	8.8	3.2	25	32	28	167	205	179	98
17	None	9.9	3.6	101	236	111	371	303	366	71
	Diethylstilbestrol									
	3 days	9.3	3.1	148	239	125	457	326	222	81
	6 days	10.5	2.6	106	183	60	187	197	218	84

NOTE: Diethylstilbestrol, 15 mg./day, was given intramuscularly. The number of days indicates the day of the test following the institution of diethylstilbestrol.

* Expressed in per cent of infused calcium (469 mg.).

† Calculated on basis of excess calcium excretion of test day and of day thereafter on which the calciuria exceeded that of the test day.

‡ Orchiectomy performed at varying time intervals prior to the studies.

of these patients was either in the normal range (Cases 10 and 14) or extremely high (Cases 9 and 13). The urinary excretion of calcium of the four patients who were tested before and during hormone therapy decreased considerably during the phase of diethylstilbestrol administration. The calciuria of one patient (Case 7) decreased to extremely low levels and was less than 10 mg./day. The calcium retention of three patients increased during the hormone phase (Case 5, 7 and 12) while that of one patient (Case 9) remained in approximately the same high range as prior to treatment. The urinary excretion of calcium of two patients (Cases 2 and 6) who received diethylstilbestrol for two years and twenty-seven days, respectively, was low. The calcium retention of the former was in the normal range while that of the latter was extremely high.

The effect of the duration of diethylstilbestrol therapy on the retention of infused calcium was

TABLE VIII

CALCIUM TOLERANCE TESTS PERFORMED DURING REMISSION AND DURING EXACERBATION OF THE DISEASE IN PATIENTS WITH PREVIOUS ORCHIECTOMY

Case No.	Status of Disease	Serum (mg. %)		Urinary Calcium (mg./day)			Urinary Phosphorus (mg./day)			Calcium Retention* (%)
		Calcium	Phosphorus	Pre Day	Test Day	Post Day	Pre Day	Test Day	Post Day	
6	Remission									
	Diethylstilbestrol†	9.1	3.2	30	65	14	282	258	218	92
	Exacerbation									
	No treatment	9.6	3.5	193	312	178	510	516	640	73
	Diethylstilbestrol†									
	2 days	10.3	3.0	166	268	147	334	370	308	77
	7 days	10.1	3.0	231	359	147	523	498	547	71
13	Remission									
	No treatment	10.7	3.0	10	35	7	284	190	169	95
	No treatment	10.1	3.3	32	52	35	228	311	262	95
	Exacerbation									
	No treatment	10.5	3.3	160	303	127	409	323	244	70

* Expressed in per cent of infused calcium (469 mg.).
† 15 mg./day.

studied with multiple calcium tolerance tests in four patients. (Table VII.) Two tests were performed in the control phase in three patients and one test in the fourth patient. The urinary excretion of calcium was in the normal range in three patients (Cases 4, 16 and 17) and was high in one (Case 11). The calcium retention was normal in two patients (Cases 11 and 17) and high in two others (Cases 4 and 16). During the administration of diethylstilbestrol the calciuria decreased rather promptly in three of the four patients tested (Cases 4, 11 and 16) while there was no decrease of the calciuria after five days of stilbestrol therapy in the other (Case 17). Also, retention of the infused calcium became maximal rather promptly in two patients (Cases 4 and 16): the urinary excretion of calcium of each of the two patients did not increase on the day of the test, on which an infusion of approximately 469 mg. calcium was given, and there was practically no excess excretion of calcium as compared to the calciuria on the day before the calcium infusion. In the five tests performed in Case 4 during the treatment phase the calcium retention was high, ranging from 92 to 95 per cent. This may represent an increase of calcium retention as compared to the control phase, at which time the patient retained 84 and 87 per cent. The retention of 84 per cent in the first test before treatment was calculated on the basis of the excess calcium excretion of the test day and of the day thereafter, since the calciuria of the latter day exceeded that of the test day. In Case 17 the calcium tolerance tests, performed twice within six days of treatment, indicate a rise in calcium retention although the urinary excretion of calcium had not yet decreased. The calciuria continued to decrease during the stilbestrol phase in Case 11 but there was only a transient increase of the calcium retention in the first test performed on the third day of treatment, and no further increase in retention in the subsequent four tests performed in the treatment phase.

Table VIII shows the results of the calcium tolerance tests performed during phases of clinical remission and exacerbation in two patients (Cases 6 and 13). Orchiectomy had been performed in both patients in the past and both had discontinued stilbestrol medication for several months. In the phase of exacerbation, the urinary excretion of calcium had markedly increased and the calcium retention decreased. No further metabolic response could be achieved when diethylstilbestrol treatment was re-instituted.

In the forty-four calcium tolerance tests listed

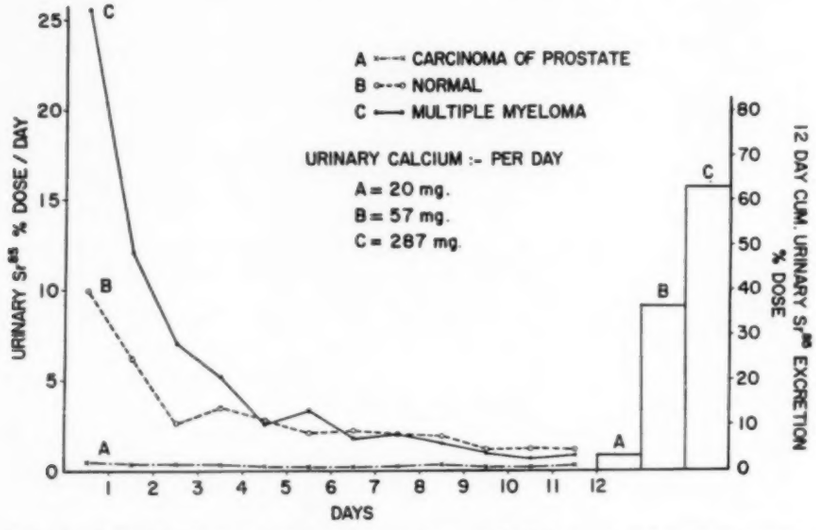


FIG. 2. Case 13. Rate of urinary excretion of Sr^{85} in man after intravenous administration.

in Tables VI through VIII, the urinary excretion of phosphorus did not decrease on the day of the test in twenty-four instances.

RADIOISOTOPE STUDIES

Figure 2 shows that the urinary excretion of Sr^{85} of a patient with carcinoma of the prostate, metastatic to bone, is extremely low following the intravenous injection of a tracer dose of Sr^{85} (Case 13). Only 0.5 per cent of the administered dose was excreted in the urine in twenty-four hours and excretion of the radioisotope continued to be extremely low during the entire study. In contrast, a patient with extensive bone involvement caused by multiple myeloma (Patient C) excreted 50 times as much, 25 per cent of the dose, in the same period of time. For purposes of comparison, the rate of urinary excretion of Sr^{85} of a patient with normal calcium metabolism (Patient B) is also shown in this graph. The low urinary excretion of calcium of the patient with carcinoma of the prostate correlates well with the extremely low urinary excretion of Sr^{85}. The twelve-day cumulative excretions of Sr^{85} again illustrate the marked metabolic differences of the three types of patients.

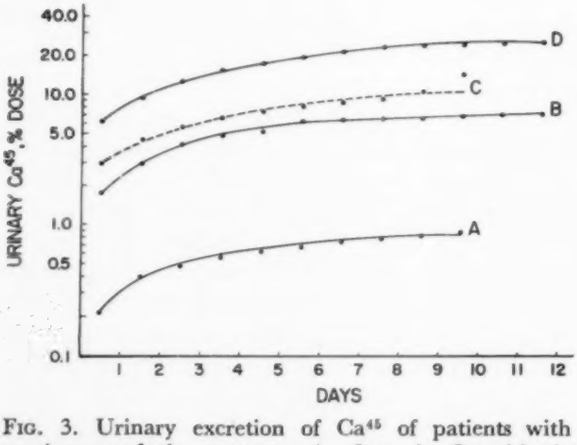


FIG. 3. Urinary excretion of Ca^{45} of patients with carcinoma of the prostate. A, Case 9. Osteoblastic metastases, low urinary excretion of calcium. B, Case 14. Osteoblastic metastases, normal urinary excretion of calcium. C, normal subject. D, Case 10. Osteoporosis, no bone metastases, elevated urinary excretion of calcium.

Figure 3 shows the cumulative urinary excretion of Ca^{45} of three patients with carcinoma of the prostate following intravenous injection of the tracer (Cases 9, 10 and 14). Considerable differences in Ca^{45} excretion were noted in these patients, depending on the state of the calcium metabolism. For example, the Ca^{45} excretion of one patient (Case 9) was extremely low: less than 1 per cent of the dose was eliminated in the urine in ten days, as compared with 12 per cent by a person with normal calcium metabolism. The urinary excretion of calcium of the former was extremely low, averaging 20 mg./day, while that of the latter was in the normal range. Similarly, the correlation between urinary excretion of calcium and of Ca^{45} is illustrated by the urinary excretion of Ca^{45} in Case 14. The urinary excretion of calcium of this patient was in the normal range and the Ca^{45} excretion was 7 per cent of the dose in ten days, comparable to that of Patient C, who had a normal calcium

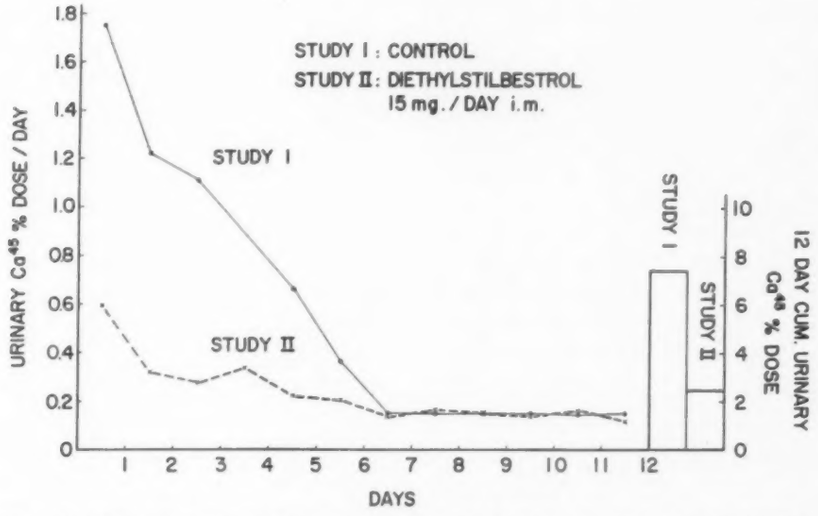


FIG. 4. Case 12. Rate of urinary excretion of Ca^{45} before and after stilbestrol administration.

metabolism. The Ca^{45} excretion in Case 10 was high, 20 per cent of the dose. This patient did not have any roentgenographic evidence of metastases to the skeleton but had osteoporosis and a urinary excretion of calcium averaging 150 mg./day at the time of this study.

The urinary excretion of Ca^{45} in two studies performed in Case 12 is shown in Figure 4. A tracer dose of Ca^{45} was injected intravenously before and during diethylstilbestrol administration. The urinary excretion of Ca^{45} was considerably higher in the control phase, study I, than in study II, which was performed after sixty-eight days of diethylstilbestrol administration. The decrease in urinary excretion of Ca^{45} accompanied a decrease in urinary excretion of calcium in the treatment phase.

The comparative metabolism of orally administered tracer doses of Sr^{85} and Ca^{45} is illustrated in Table IX. The absorption of Ca^{45} in Case 1 was low and the ratio of the absorbed Ca^{45}/Sr^{85} was 0.88. The urinary excretion of Ca^{45}, expressed in per cent of the administered dose, was approximately one-tenth of that of Sr^{85}. In Case 5 the ratio of the Ca^{45}/Sr^{85} absorption was 3.8 and the excretion of Ca^{45} was approximately 2.5 times as high as that of Sr^{85}. The urinary excretion of Ca^{45} in this case was relatively high in the study performed in the control phase. The Sr^{85} excretion was considerably lower in the study carried out after thirty days of diethylstilbestrol administration, at which time the urinary excretion of calcium had considerably decreased (30 mg./day vs. 120 mg./day). However, the urinary excretion of Sr^{85} in this case, expressed in per cent of the *absorbed* dose, was approximately 1.6 times as high as that of Ca^{45}.

TABLE IX
ABSORPTION AND EXCRETION OF SR^{85} AND CA^{45} FOLLOWING THE ORAL ADMINISTRATION OF THE TRACERS (TWELVE-DAY STUDY)

Case No.	Ca^{45} (% administered dose)		Sr^{85} (% administered dose)		Urinary Excretion (% absorbed dose)	
	Absorption	Urinary Excretion	Absorption	Urinary Excretion	Sr^{85}	Ca^{45}
1	22	0.06	25	0.55	2	0.27
5	50	6.4	13*	2.6*	20*	12.8

NOTE: The tracer doses were administered simultaneously in Case 1 and separately in Case 5. Excretions are cumulative for twelve days.
* Study performed after thirty days of diethylstilbestrol administration (15 mg./day).

COMMENTS

Few reports are available in the literature on the protein and mineral metabolism of patients with metastatic carcinoma of the prostate, and on the effects of therapy. A short term calcium balance study of two untreated patients with carcinoma of the prostate, covering two and three days, respectively, appeared in 1946 [*24*]. Data on the metabolic effects of treatment of patients with carcinoma of the prostate were presented in 1947 by Aub, Tibbets and Nathanson [*25*]. Metabolic balances of five patients with advanced carcinoma of the prostate were

presented in 1950 by Schilling et al. [*11a*]. The results obtained in an extensive study carried out in one of these patients before and during estrogen therapy were subsequently recorded by Schilling and Laszlo [*11b*].

The balance data reported in the present communication confirm and extend the previously described findings obtained in the study of the patient reported on from this institution [*11b*]. The calcium metabolism of patients with active bone disease due to metastatic carcinoma of the prostate differs from that of patients with bone involvement caused by other tumors, e.g., carcinoma of the breast, thyroid or lung [*26*], which are either predominantly lytic or of the mixed type. The extremely low urinary excretion of calcium of untreated patients with widespread carcinoma of the prostate metastatic to bone and the normal calcium balance during low calcium intake indicate the great avidity of the skeleton for calcium. The low calciuria in the presence of normal serum calcium levels suggests that the filtered calcium load is within normal limits but that renal tubular reabsorption of calcium is increased. This tendency to retain calcium becomes even more evident when the calcium tolerance test is performed; in persons with normal mineral metabolism, as tested by the balance technic, an average of 71 per cent of the infused calcium is retained and 29 per cent is excreted, while a considerably higher proportion is frequently retained by patients with carcinoma of the prostate and metastatic bone disease. The calcium retention of seven of the fifteen patients tested was greater than 75 per cent and three of these retained from 93 to 97 per cent of the infused dose.

The urinary excretion of phosphorus decreases on the day of the calcium tolerance test in normal subjects [*13–15,27–30*]. The lack of decrease of urinary excretion of phosphorus in approximately 50 per cent of the calcium tolerance tests performed in these patients in the control and treatment phase is of interest since this has been observed also in patients with hyperparathyroidism [*28,30–32*]. None of the patients with carcinoma of the prostate had any clinical, chemical or anatomical evidence of hyperfunction of the parathyroid glands.

In the phase of diethylstilbestrol therapy the urinary excretion of calcium decreased in all patients studied except one (Case 17) in whom this determination was performed for only seven days after the institution of treatment. Of interest is the fact that administration of estrogens leads to marked lowering of the urinary excretion of calcium in normocalciuric patients so that excretion levels of less than 10 mg./day were encountered. The retention of infused calcium, which was in the normal range or higher prior to treatment, frequently increased further under the influence of estrogen. The hormone-induced decrease in urinary excretion of calcium and the increase in calcium retention correlated well with the relief of bone pain. This increase became maximal within a few days of therapy and was observed in those patients who responded favorably to hormone therapy within a short period of time. It seems that the already dense skeleton, the site of extensive osteoblastic metastases, tends to retain even more calcium during hormone administration. Since the retained calcium is probably deposited in the skeleton, one wonders whether or not the tumor cells located in bone assume osteoblastic activity and utilize calcium for new bone formation [*33–36*]. Also, it was noted that if clinical and metabolic changes did not occur within a few days of hormone therapy prolonged administration of stilbestrol did not lead to further increments of calcium retention or to better clinical palliation. The poor clinical response of one patient (Case 11) to treatment was accompanied by a lack of increased calcium retention during estrogen therapy, although the urinary excretion of calcium markedly decreased. (Table VIII.) The divergence of the two parameters, namely, the decrease of the urinary excretion of calcium and the increase of calcium retention may indicate that the calcium excretion reflects bone resorption while the calcium retention measures bone formation. Although both parameters are useful for objective evaluation of the effectiveness of therapy, the increase in calcium retention, on performing the calcium tolerance test in the early phase of treatment, may be a better prognostic indicator since a rise in calcium retention was frequently accompanied by marked clinical improvement. Exacerbation of the disease following discontinuation of stilbestrol therapy correlated with an increase of urinary excretion of calcium in two patients during the terminal phase of illness, and re-institution of hormone therapy did not result in further clinical or metabolic improvement.

The effect of estrogen on the skeletal system of experimental animals has been extensively described by Gardner and Pfeiffer [*37*] and of

patients with osteoporosis by Albright and Reifenstein [*38*]. This hormone was found to have different effects in different species: decrease of bone resorption was found in rats [*39, 40*] and increased calcium deposition in chicks [*41*]. In patients with metastatic carcinoma of the prostate both effects seem to be operating, since the urinary excretion of calcium decreases and retention of infused calcium increases under the influence of female hormone. Whether or not these effects are in part mediated by changes in tubular reabsorption of calcium cannot be stated from these studies. The decline in urinary excretion of calcium and the improvement of the calcium balances of patients with metastatic carcinoma of the prostate during the administration of estrogen is in agreement with observations made in patients with osteoporosis [*38*], in those without osteoporosis [*42*], in patients with multiple myeloma [*43–46*] and in those with carcinoma of the breast metastatic to bone [*47,48*]. The effect of this hormone on the alkaline and acid phosphatase has been extensively described in the literature. Woodard described an increase of the alkaline phosphatase during the early phase of estrogen administration (alkaline phosphatase "flare") which is followed by a return to lower levels in the later phase of treatment [*10,49*]. A decrease of the acid phosphatase in patients with carcinoma of the prostate induced by estrogenic hormones has been reported by several investigators [*3,5,10,50,51*]. An increase of the alkaline phosphatase and a decrease of the acid phosphatase was observed in a large number of the patients reported on here, although this was not a consistent finding during the phase of estrogen administration. The rise of the alkaline phosphatase is consistent with increased osteoblastic activity and possible new bone formation. The decrease of acid phosphatase is presumably due to inhibition of tumor growth.

The metabolic studies carried out in two patients with carcinoma of the prostate before and after orchiectomy indicate marked retention of nitrogen following this procedure. Also, a considerable decrease in urinary excretion of calcium was observed in one of the patients (Case 6). Since the effect of orchiectomy in normal males is not known, the influence of this procedure on the prostatic tumor cannot be differentiated from that on normal tissues. Nitrogen retention has been described in neoplastic disease in experimental animals and man [*26,46,52,53*]. No reference to the metabolic effect of orchiectomy in man could be found in the literature. Changes in metabolism induced by castration have been described in experimental animals. In adult albino rats, castration led to impaired food intake and inhibition of weight gain several months after this procedure [*54*]. Kochakian [*55*] found slight nitrogen retention following a transient period of nitrogen loss in orchiectomized rats.

The results obtained with tracer studies, carried out with Sr^{85} and Ca^{45}, correlated well with the data obtained by balance studies. The extremely low urinary excretions of Sr^{85} and Ca^{45} following the intravenous and/or oral administration of these tracers again indicate the marked tendency to mineral retention of patients with prostatic carcinoma and osteoblastic metastases. Also, the difference in urinary excretion of radiostrontium was much greater than the difference in urinary excretion of calcium in different types of patients. For instance, the urinary excretion of calcium of a patient with normal calcium metabolism was 2.5 times as high, that of a patient with multiple myeloma 15 times as high as that of a patient with carcinoma of the prostate, whereas there was a twenty- and fiftyfold increase of the urinary excretion of radiostrontium in the two patients, respectively, as compared to that of the patient with carcinoma of the prostate. Similarly, differences in calcium metabolism were also defined more clearly by Ca^{45} studies than by the urinary excretion of calcium or calcium balances in patients with different types of derangements of calcium metabolism [*15*]. These observations indicate that the tracer technic is a more sensitive tool for characterization of abnormalities of calcium metabolism [*15–19*] than the determination of metabolic balances.

Studies on the comparative metabolism of orally administered tracer doses of Ca^{45} and Sr^{85} carried out in a large number of patients have revealed preferential absorption of Ca^{45} from the gastrointestinal tract and preferential urinary excretion of Sr^{85} [*19,56*]. The considerably higher absorption of Ca^{45} than of Sr^{85} (50 vs. 13 per cent) in Case 5 and the higher urinary excretion of Sr^{85} than of Ca^{45} in terms of the *absorbed* dose are in agreement with these findings. This agreement is noteworthy in this case since the Ca^{45} study was carried out during the more active phase of illness (control phase), at which time the urinary excretion of calcium was approximately four times as high as in the treat-

ment phase, when the Sr^{85} study was performed. The reason for the low absorption of Ca^{45} in Case 1 is not clear and may possibly be due to delayed intestinal passage time since relatively high amounts of radioactivity, 8.8 per cent of the dose, were still recovered in stool specimens on the twelfth day of the study. Although the ratio of absorption of Ca^{45} and Sr^{85} was of approximately equal magnitude in this case, there was preferential urinary excretion of Sr^{85} in terms of the *absorbed* fraction of the dose.

SUMMARY

1. Sixteen patients with bone metastases secondary to carcinoma of the prostate and one patient without bone metastases were studied under controlled dietary conditions. Metabolic balance studies of calcium, phosphorus and nitrogen, calcium tolerance tests and radioisotope studies were performed.

2. A marked tendency to calcium retention was noted in patients with osteoblastic metastases. The urinary excretion of calcium of untreated patients frequently was extremely low. Even in the active stage of bone disease, the calciuria was rarely as high as in patients with bone involvement caused by other tumors. The calcium balance of six untreated patients was normal on low calcium intake and was negative in one patient. Calcium retention, as indicated by the calcium tolerance test, was greater than normal in a large number of patients.

3. The urinary excretion of radiocalcium and radiostrontium was extremely low in some patients. The magnitude of the tracer excretions depended on the state of the calcium metabolism of the patient.

4. Estrogen therapy resulted in a decrease in urinary excretion of calcium and improvement of the calcium balances. Hormone-induced changes of calcium metabolism were paralleled by changes in Ca^{45} excretion. The retention of infused calcium increased further during estrogen therapy. There was a good correlation between the changes in calcium metabolism induced by estrogen and the clinical response. An increase in calcium retention as estimated by the calcium tolerance test may be a better objective indicator of the effectiveness of therapy than the decrease in urinary excretion of calcium.

5. The urinary excretion of calcium of six patients, in whom orchiectomy was performed at varying time intervals prior to the balance studies, was either in the normal range or extremely low. The calcium balances were normal on a low calcium intake. The calcium balance of one patient was negative due to high urinary excretion of calcium.

6. Balance studies performed in two patients before and after orchiectomy revealed marked nitrogen retention following this procedure. The urinary excretion of calcium of one of these patients decreased to half the control excretion.

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Hypersensitivity to Para-Aminosalicylic Acid*

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PARA-AMINOSALICYLIC acid (PAS) is widely used in the treatment of all forms of tuberculosis. Hypersensitivity to this drug occurs with a frequency that renders its diagnosis and management of some importance. While in many respects this reaction resembles that produced by several other drugs, it has features which are sufficiently defined to be of value. An analysis of published observations and a study of forty-eight previously unrecorded cases observed in the Bellevue Hospital Chest Service form the basis of this report.

REVIEW OF PREVIOUSLY PUBLISHED CASES

The history of a patient reported on by Hemming and Stewart in 1949 is believed to contain the first detailed description of this disorder [*1*]. The condition has been mentioned in at least 150 publications, 115 of these containing case histories [*1,2,4–10,12–79,82–85,88,89,91–122*]; most reports refer to single instances or to a small number of patients, the largest series hitherto available contained fourteen cases [*2*]. The 229 cases previously reported and included in this review have all been well documented, and in most cases the diagnosis has been confirmed by a second response to the drug.

When stated, the calculated incidence has varied from 0.28 per cent to 5 per cent [*3–7*]. Most reports have described adult patients but cases have also been observed in pediatric practice [*7–10*]. There has been no suggestion of racial predisposition. There is evidence that hypersensitivity to many drugs is more common in persons with a history of allergic phenomena, and such susceptibility has been demonstrated in the guinea pig by selective breeding [*11*]. No relationship of this type has been noted in the case of PAS.

The reaction to this drug has occurred from the first to the seventy-fourth day of treatment [*5,7,12*], the average time being the twenty-fourth day. In more than half the cases the onset was between the beginning of the third and the end of the fifth week. The most prominent features are listed in Table 1 in which the findings in the previously recorded cases are compared with those in the two groups to be described.

Fever has been the most common early manifestation, being absent in only five cases [*5,13–15*]. Conjunctivitis with lacrimation, burning of the eyes, headache and joint pains have occurred frequently. The skin rash, prominent in 167 cases, was most often generalized, erythematous, maculopapular and pruritic, commonly starting over the face and neck. A localized form has also been described. Desquamation of the skin, from a fine branny scaling to coarse exfoliation, has been seen in severe cases. An urticarial type of lesion has been described infrequently. This has occurred earlier than the more common manifestations, the usual symptoms appearing at a later date. Lymphadenopathy has been noted relatively infrequently. Jaundice has been described in fifty-three cases [*2,4,6–8,14,16–56*], usually preceded by other symptoms although

TABLE 1
COMPARISON OF RECORDED CASES AND TWO GROUPS OF CASES AT BELLEVUE HOSPITAL

Findings	Recorded Cases (229)	Bellevue Hospital Cases	
		Group 1 (31)	Group 2 (17)
Fever	224	31	16
Skin rash	167	21	11
Lymphadenopathy	51	7	0
Jaundice	53	11	0
Hepatomegaly	61	11	0
Leukocytosis	73	13	8
Eosinophilia	64	12	8
Abnormal lymphocytes	41	5	11
Abnormal hepatic function	68	11	2
Sensitivity to streptomycin	28	1	1
Sensitivity to isoniazid	10	2	1
Desensitized	62	16	15
Deaths	11	0	0

* From the Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, and the Chest Service of Bellevue Hospital, New York, New York.

skin lesions were occasionally absent. Jaundice appeared from one to twenty-five days after the onset of the reaction, in a large percentage of the cases during the second week. In several cases it was precipitated by testing with a relatively large amount of the drug or from the inadvertent reinstitution of the regular dosage. In one case it resulted from the administration of 5 gm., one year after the original episode [*54*]. In patients in whom the drug was stopped early and while symptoms were mild the temperature fell to previous levels usually within twenty-four hours. When interruption of chemotherapy was delayed, resulting in more severe symptoms, this took longer, but the temperature usually returned gradually to pre-existing levels within one week.

A few reports have described less commonly observed manifestations. Roentgenographic findings attributed to Löffler's syndrome have been recorded in thirteen cases [*5,12,27,32,45,48,57–60*]. These have been observed from the first to the tenth day of the reaction. Transient renal impairment has been noted in eight cases [*18,34–36,46,60–63*]. In one case, in association with severe desquamation, there was an ulcerative stomatitis [*18*]; in two cases, there was complete alopecia which was transient [*19,61*]. Laryngeal stridor has been described [*64*]. The appearance of pleurisy with effusion and ascites [*8*], and of meningitis [*65*] are the only instances in which involvement of serous membranes has been suggested. One case of the Guillain-Barré syndrome was encountered [*61*]. Blood dyscrasias, aplastic and hemolytic anemia, thrombocytopenia and agranulocytosis have been described [*4,40,66–69*]; of these disorders thrombocytopenia is the only one which was clearly proved to be caused by hypersensitivity to PAS [*67*].

In twenty-eight cases there was apparently coexisting hypersensitivity to streptomycin [*5,6, 10,14,18,21,32,36,40,46,55,57,66,70–76*], and in ten to isoniazid [*27,37,45,56,58,72,77–79*]. There was one possible but unconfirmed case of associated hypersensitivity to viomycin [*40*]. However, it is not possible to calculate accurately the incidence of multiple drug hypersensitivity. In only one case could streptomycin, isoniazid and PAS all be incriminated [*72*]. Reactions have been encountered in patients under treatment with one drug, most commonly isoniazid [*80,81*].

Eleven deaths have been recorded. Hepatic damage was the cause in seven fatalities [*17,26, 29,30,36,37,39*]; in one patient death resulted from acute shock soon after a test dose of 5.5 gm. had been administered [*82*]; one patient had hemorrhagic encephalitis [*70*]; one patient had hemorrhages in the myocardium, petechial hemorrhages in the brain and adrenocortical degeneration [*83*]; and one patient had aplastic anemia [*66*]. Although a second drug had been given in each of the last three cases, PAS was probably the sensitizing agent. Because of the tendency to report only severe reactions, it is not possible to estimate the incidence of damage to the liver or the mortality rate.

Detailed laboratory data are available in relatively few cases. Leukocytosis and eosinophilia have been described as characteristic findings. White blood cell counts of more than 50,000 per cu. mm. have been found, with eosinophilia up to 70 per cent of the total white cells. Lymphocytosis has been observed with abnormal lymphocytes of the Downey cell types I, II and III, most commonly type I [*2,6,27,77,84*]. The finding of the LE cell phenomenon, demonstrated by the Hargrave technic, has been reported in one case [*85*]; but clinical manifestations suggesting the presence of one of the so-called collagen diseases have not been described. Disturbed liver function has been indicated by the abnormal results of the cephalin flocculation test, thymol turbidity test, serum alkaline phosphatase, icterus index and serum proteins. These have also been noted in cases without clinically apparent jaundice. Histologic examination of the liver has demonstrated destruction of liver cells and some stasis of bile in the canaliculi [*28*]. There has been more parenchymal damage and less obstruction than in cases of jaundice produced by chlorpromazine [*86*]. Histologic study of enlarged lymph nodes has revealed hyperplasia of the reticuloendothelial elements with loss of the normal architecture, an increase in lymphocytes and eosinophils, and the presence of immature lymphocytes have also been noted [*2,4*]. Examination of sternal marrow has shown a shift to the left in the myeloid series, with an increase in eosinophils [*2*].

Methods of management have varied widely. The diagnosis has not always been confirmed by tests, but often by the reinstitution of therapy. Skin tests have been used, but most observers have found this method to be unsatisfactory as compared to the oral method of administration. Sixty-two of the 229 patients were successfully desensitized. In many cases no attempt was made

to resume treatment, particularly where symptoms had been severe. However, this has often been accomplished after recovery from jaundice. Dixon [*33*] recommended a delay of several weeks before attempting desensitization because of the danger of precipitating damage to the liver. The amount of drug used in testing has ranged from 500 mg. to 4 gm., the course of desensitization beginning with 10 to 500 mg; this took from fourteen to fifty-four days to complete [*2,4,5,6,32,87*]. Houghton [*48*], Marsch [*73*] and others have described the use of steroid therapy to "cover" the course of desensitization. Francis, Gupta and Palmer [*88,89*] have reported rapid desensitization in ten patients by this method; this was accomplished in four to seven days. Several patients on steroid therapy together with drugs including PAS have manifested evidence of hypersensitivity upon discontinuation of the steroid [*90*]. In one patient fever developed while cortisone, 100 mg. daily, was being given with streptomycin, isoniazid and PAS; after the dosage of the steroid was reduced to 50 mg. daily, a rash appeared [*92*]. There is little information about the duration of the hypersensitive state but it has been known to persist in two patients for periods of eight and twelve months [*54,92*].

OBSERVATIONS ON NEW CASES

Clinical Material and Methods. Forty-eight previously unpublished cases of hypersensitivity to PAS have been studied. These patients have been divided into two groups; in group 1, thirty-one patients were seen prior to September 1957, and in group 2, seventeen patients were observed since that data. The findings in the two groups are included in Table 1. The earlier case reports were reviewed in retrospect; these patients had been managed by many physicians, and by several different methods. Since September 1957, all patients in whom the diagnosis was suspected were seen and closely observed by us. When the diagnosis appeared reasonably certain, all drugs being administered were immediately discontinued; this included drugs being given for the treatment of conditions other than tuberculosis. Steps were taken to insure against the inadvertent reinstitution of any of these drugs. A four hourly temperature record was instituted and a complete physical examination carried out. A roentgenogram of the chest was obtained. Samples of peripheral blood were collected for total white cell and differential counts, examination of the stained

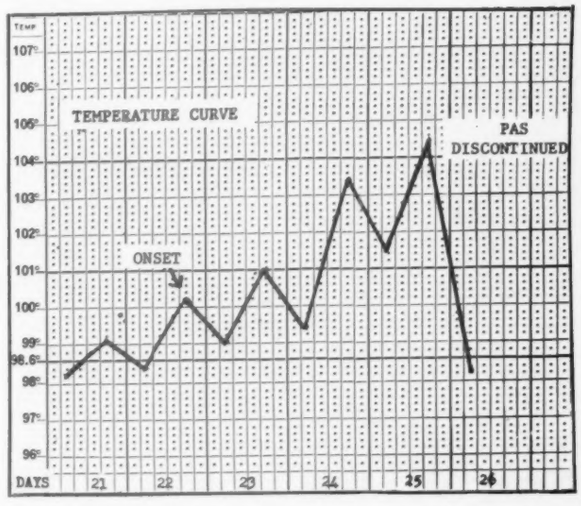


FIG. 1. Typical temperature curve at onset of reaction.

smear, and for tests of hepatic function; these included the total serum proteins, albumin and globulins, the icterus index, alkaline phosphatase, cephalin flocculation, serum bilirubin and thymol turbidity tests. These laboratory studies were repeated at intervals. When symptoms had subsided the diagnosis was confirmed by the response of the patient to a small amount of the drug administered orally, as a challenge.

CLINICAL FINDINGS

Of the forty-eight patients, the age and sex distribution conformed with that of the population on the service. The racial trend was not in keeping with that in general, the condition being encountered in white patients twice as frequently as in the Negro. A history of allergy was obtained in fourteen patients, suggesting an incidence which is considerably higher than the generally accepted figure of 10 per cent in the general population. The incidence of hypersensitivity, as calculated from the patients in group 2, was 2 per cent. The time of onset in relation to the date of commencement of therapy ranged from eight to sixty-one days, with an average of twenty-three days. In more than half of the cases the reaction occurred between the twentieth and thirtieth days of treatment.

The severity of the early symptoms varied considerably; the most common initial manifestation was a rise in temperature. Figure 1 illustrates a typical temperature curve; this has usually been described in the past as an abrupt elevation. An initial slight rise has commonly been observed, and this is present in several of the temperature curves which have been

published, although it has not been commented upon as characteristic. Only one patient was encountered in whom there was absence of fever throughout the course. The pyrexia commonly reached a level of 102° to 104°F., and in some of the patients in group 1, when the drug had not been discontinued promptly, the fever progressively increased, although somewhat intermittently. In all patients in group 2 the temperature fell to the previous range within twenty-four hours of discontinuing therapy. In four of the patients in group 1 whose symptoms were more severe, this took up to three days.

The most common complaint related to involvement of the skin, varying in degree from a sensation of prickling to the presence of a rash. This was usually erythematous, maculopapular and pruritic. It was observed within two to three days of the onset of the fever in the thirty-two patients in whom it occurred, twenty-one in group 1, eleven in group 2. The rash commonly appeared first on the trunk and, according to its severity, spread in some patients to involve the entire body surface including the palms of the hands and soles of the feet. A localized form of skin lesion has not been observed. In cases of mild involvement of the skin recovery was usually complete within a few days of discontinuing therapy. In a few patients in whom this manifestation was more severe the course was more prolonged, the lesions taking up to eight weeks to clear completely. In these patients, resolution was usually accompanied by a branny desquamation. In two patients in group 2 the skin lesion was severe and was accompanied by coarse desquamation. In one patient in group 1 it was associated with total alopecia, from which there was complete recovery. Lymphadenopathy was observed in seven patients in group 1; the glands of the cervical region were most commonly involved, the enlargement appearing three to four days after the start of the reaction. This was not encountered in any of the patients in group 2. Jaundice with hepatomegaly occurred in eleven of the thirty-one patients in group 1, appearing between four and thirty days after the start of the reaction. In more than half of these patients the jaundice appeared later than fourteen days, and in only three cases was the onset earlier than ten days. It usually persisted for two to three weeks. Only once did it occur in a patient who did not exhibit any involvement of the skin. Jaundice has not been observed in the seventeen cases in group 2, nor has hepatomegaly been discovered in its absence. Splenomegaly has not been encountered. Other symptoms of a more minor nature were occasionally seen in the patients in group 2; three patients complained of headache, the cerebrospinal fluid examined at this time revealed no abnormalities. One of these patients had conjunctivitis. In no case did the roentgenogram of the chest taken at the height of the reaction show any change.

Laboratory Data: An increase in the total white cell count, ranging from 15,000 to 50,000 per cu. mm., occurred in half of these patients; in eight patients the count exceeded 20,000, seven were in group 1, one was in group 2; eosinophilia up to 30 per cent of the total white cell count usually accompanied this increase. In group 2, abnormal lymphocytes of the Downey cell type, up to 50 per cent of the total, were observed in eleven patients. These were commonly discovered by the third day of the reaction, and in most of these cases there was also a relative lymphocytosis. A rise in the total white cell count, with eosinophilia, usually occurred within the next few days. Abnormal lymphocytes were noted in only five cases in group 1, but attempts to find them were not always made. Search was made for the LE cell phenomenon which was not found in any case. Disturbance of hepatic function as reflected by abnormal results of the icterus index, alkaline phosphatase and cephalin flocculation tests was observed in the eleven cases of jaundice. This took from six to eight weeks to disappear. Abnormalities of lesser degree were observed in two cases without jaundice, these disappeared within four weeks. Heterophil antibodies were absent from the blood in the seventeen cases in group 2. Histologic examination of lymphoid tissue obtained during the reaction revealed reticuloendothelial hyperplasia with an increase in eosinophils. This change is not regarded as specific. A biopsy specimen of the liver was obtained in four patients in whom jaundice developed. There was variation in the size, shape and staining properties of the hepatic cells and nuclei. Some cells had clumped eosinophilic cytoplasm, in others the cytoplasm was vacuolated; giant cells were seen here and there, and some cells had double nuclei. There was some apparent increase in connective tissue in the portal areas extending out along the cholangioles; in these areas there was a diffuse infiltration by lymphocytes and

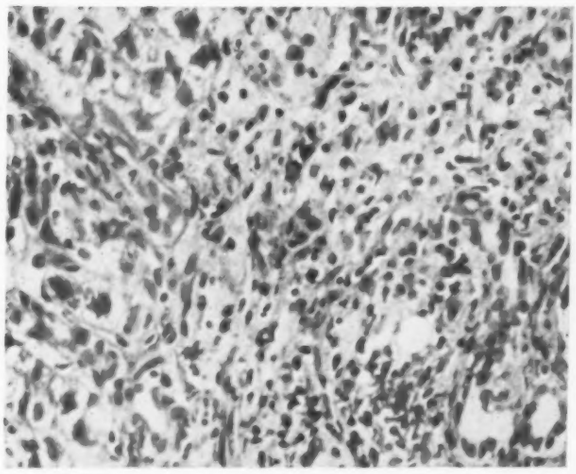


FIG. 2. Histologic section of liver early in the course of jaundice.

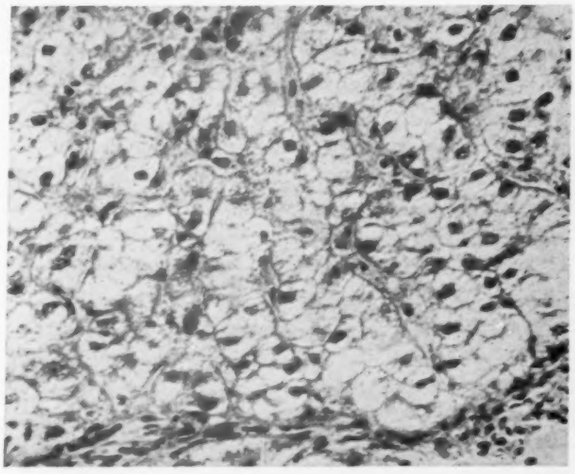


FIG. 3. Histologic section of liver from the same patient, two weeks later.

mononuclear cells, with occasional polymorphonuclear leukocytes. There were numerous bile plugs in the canaliculi. The histologic section from one patient is shown in Figure 2. In this patient examination two weeks later (Fig. 3) showed the liver cells and their nuclei to be much more uniform, the cells containing large amounts of glycogen. Occasional giant forms were observed, suggesting a continuing process of regeneration. The amount of pigment in the liver cells had diminished, although the Kupffer cells now contained a golden-brown pigment. The bile canaliculi were free of bile plugs. The change previously interpreted as fibrosis in portal and cholangiolitic areas was much diminished; except for a few mononuclear and occasional polymorphonuclear leukocytes, some of which were eosinophilic, the infiltrative reaction had subsided. The marked change towards the normal was in keeping with the clinical course.

MANAGEMENT

Although the possibility exists that there may be hypersensitivity to one or more of the drugs, depending on the combination in use, PAS is the most likely offender because of the higher incidence of hypersensitivity to it. In group 2, testing with 1 gm. given orally was therefore carried out as soon as symptoms arising from the initial reaction had subsided. In confirmed cases the severity of the response to this challenge was variable, just as were the initial symptoms. A varying degree of hypersensitivity among these patients was suggested by the fact that repeated testing with amounts of drug smaller than 1 gm. illustrated a marked difference in the dosage necessary to produce the response. In some cases, more than 1 gm. was necessary. A rapid rise in temperature, often associated with the abnormalities in the peripheral blood already noted, was taken as sufficient indication of response.

When the patient was free of symptoms following the challenge doses, a course of desensitization was commenced. This was completed before other drugs to be used in combination were reinstituted. In the thirty-one patients in group 1 there was no standard form of management, with results that were not always satisfactory. In the patients in group 2, 10 mg. was uniformly used to start the course. Amounts of less than 1 gm. were given in a single dose, after which the drug was administered in divided doses in the usual way. This was doubled every two days, provided no symptoms appeared. When a reaction was indicated, usually in the form of a temperature rise with or without mild involvement of the skin, the course was modified, depending on the severity of these symptoms, by giving an equal or smaller amount on the following day. Patients in whom the initial symptoms were severe or who demonstrated a marked response to testing were those in whom difficulties of this type arose during the process of desensitization. On the other hand, after a mild reaction desensitization tended to proceed more rapidly. A critical point appeared to be at one to one and a half gm.; once this was passed, further difficulty was unusual. For the purpose of testing and during desensitization an aqueous solution of the sodium salt was given. Great care was taken

in its administration; in the patients in group 2 the solution was administered in all instances by one graduate nurse who assisted in their management. Sixteen patients in group 1 were successfully desensitized, fifteen in group 2; the other two patients in group 2 left the hospital against advice before this could be accomplished. One patient was desensitized one year after the initial reaction. Repeated challenge doses during the year demonstrated a diminution in the degree of sensitivity; early in the course, 10 mg. was sufficient to produce a response, while at the end of the year the amount necessary was 750 mg. Of the eleven patients in whom jaundice was a complication, desensitization was completed in seven. In two patients in group 1 particularly severe symptoms were exhibited, one related to the skin lesion and the other to hepatic involvement; steroid therapy was employed as an adjunct during the process of desensitization. This form of management has not been used in the patients in group 2 because methods of desensitization formed part of the investigation. It is considered that it could have been employed to advantage in two of the seventeen patients. It has been confirmed that patients hypersensitive to the type of PAS used will react to other forms of sodium, calcium and potassium PAS; testing with calcium benzoyl PAS was not carried out. In those patients who also manifested evidence of hypersensitivity to streptomycin or isoniazid, testing was performed at a time when no other drug was being administered.

Two patients were also sensitive to streptomycin, three to isoniazid; in the treatment of most of the patients two drugs were employed. Of interest is the fact that the patient in group 2 whose symptoms were most severe, and who reacted to 10 mg. of PAS as a test, did not show any hypersensitivity to the administration of streptomycin or isoniazid. Desensitization to the other drugs was completed more rapidly and with more ease than in the case of PAS, perhaps because the therapeutic amount is much smaller. As a test for isoniazid, 50 to 100 mg. was given, 10 mg. being used to start desensitization; in the case of streptomycin, 100 mg. to test and 10 mg. to initiate desensitization.

COMMENTS

Although there are many disadvantages associated with the administration of PAS, it is seldom omitted from the drug combination employed in the initial treatment of tuberculosis. While the therapeutic efficacy is relatively slight, its effect in delaying the emergence of resistant organisms justifies its inclusion. In spite of the low incidence of this complication, it must be encountered fairly frequently owing to the fact that the drug is used so extensively. Attention has been drawn to the desirability of having patients hospitalized during the early part of the course of chemotherapy for tuberculosis [*123*]; exclusion of hypersensitivity reactions and the need of their management are good reasons. Patients in whom treatment is started outside the hospital should be warned of the possibility of this complication.

Drug hypersensitivity, in the form under consideration, is thought to be of the delayed type. A period of exposure to the drug is necessary for its development, but once the hypersensitivity has been initiated the patient will react to small quantities of the drug in a manner closely resembling the original episode. Precise knowledge of the mechanism of production of this type of sensitivity is lacking, nor is the process involved in the production of the pathologic changes understood. There is therefore little basic information which might be applied to the understanding of PAS hypersensitivity.

There are features which are sufficiently well established to suggest the diagnosis. The time of onset in relation to the start of treatment is important. The appearance of fever of 102° to 104°F. in a patient previously afebrile, especially if occurring during the fourth week of treatment, and particularly if preceded by a gradual rise over the previous two days, should arouse strong suspicion of PAS hypersensitivity. This is reinforced by the complaint of itching of the skin or the appearance of a rash. Under these circumstances it is preferable to discontinue the administration of drugs, rather than risk increase in the severity of the symptoms. The rapid disappearance of symptoms which follows the prompt cessation of therapy further strengthens the diagnosis. That early discontinuation is of great importance has been abundantly demonstrated. In the patients in group 2 of this study, when this was effected by the second day at the latest, fever and involvement of the skin were the only symptoms; in only two of these patients was the latter symptom responsible for more than slight and transient discomfort. That there is not necessarily a correlation between the severity

of involvement of the skin and hepatic damage was demonstrated by the fact that the two patients with severe skin lesions had no clinical jaundice, although one of these had slight abnormality as reflected in the tests of hepatic function. In one patient, jaundice occurred in the absence of involvement of the skin. In half of the patients in group 1 the administration of PAS was continued for more than two days after the start of the reaction, the average time of discontinuation being the fourth day; in the recorded cases, in which the information is available, many days often elapsed before the cessation of therapy. In these two groups of cases it seems fairly certain that the more severe manifestations can be directly related to this delay. In the recent group of patients studied, when the diagnosis was made promptly and when methods of management were consistent, the decreased severity of manifestations was conspicuous. It appears likely that patients with a severe skin reaction occurring as an early manifestation are those in whom the drug is commonly discontinued promptly; in patients with mild initial symptoms, drug administration is likely to be continued for a longer period, with the added danger of more serious complications such as hepatic damage.

The amount of drug used in testing and in beginning the course of desensitization can be estimated according to the severity of the initial reaction. The ideal amount to be used in testing is that quantity which will effect the minimum response; this will avoid delay during recovery from any symptoms so produced. Confirmation of the diagnosis by this method is essential; much uncertainty will be avoided and time saved by this procedure. Fewer difficulties will be encountered if the amount used as a challenge is kept low, for example 250 mg. This may be increased subsequently if no response ensues. Of the patients in group 2, some were shown to react to amounts much smaller than 1 gm., with less severe symptoms after the test. When symptoms have subsided, no delay is necessary before confirming the diagnosis. Most patients in whom serious symptoms have followed testing, even with relatively small amounts of the drug, have been patients in whom the diagnosis was delayed, and in whom administration of the drug had been continued for several days. It is recommended that the amount used to initiate desensitization be confined to 10 mg. although smaller amounts may be necessary in a few patients. In some patients, a larger amount may be employed, but the course is more uniformly uncomplicated by the method recommended. No effect on symptoms or increase in the ease of desensitization has been observed following the simultaneous administration of antihistamine drugs. This lack of influence has been demonstrated in the case of penicillin hypersensitivity by Coleman and Siegal [*124*] and others. Adjunct steroid therapy has been recommended as treatment for severe manifestations; this will also reduce the difficulty of desensitization in these patients and permit a more rapid return to the regular dosage. The rapid method of desensitization using ACTH, as described by Francis and Gupta [*88*] and Gupta and Palmer [*89*], is worthy of consideration. However, the methods employed in the seventeen patients in group 2 produced little delay in the institution of effective treatment, desensitization being completed within twenty-four days; in none of the patients in the group did this result in any deleterious effect and the hazards of steroid therapy were avoided. It is considered that PAS is of sufficient importance in the chemotherapy of tuberculosis to warrant such slight inconvenience.

It has been suggested that allergy to PAS may predispose a patient to a similar reaction resulting from the administration of another drug, and that this is a result of the effect of hypersensitivity to PAS. In no case where hypersensitivity to more than one drug was observed could it be explained as a phenomenon of "nonspecific flare-up." When multiple drug sensitivity was demonstrated, a reaction to the second agent could be elicited after desensitization of the patient to PAS. There is, however, a strong suggestion that patients who exhibit manifestations of hypersensitivity to PAS are more likely to do so also in the presence of other drugs. It may, therefore, be implied that these patients have a more than usual tendency to develop allergy to many substances, as suggested by the previous history.

SUMMARY

A review of the extensive literature has disclosed 229 previously published cases of hypersensitivity to PAS therapy. The pertinent information available from these reports is presented, and to this are added the relevant facts from forty-eight new cases.

Despite the wide variety of clinical and labora-

tory findings reported, a large percentage of patients exhibit manifestations which fall within a fairly fixed pattern. Fever and involvement of the skin are the most common. The most serious effect of this disorder is hepatic damage, which may be fatal. With prompt recognition, verification of the diagnosis and proper methods of management, this complication produces only slight inconvenience during the course of treatment.

Until PAS therapy assumes a position of less importance than at present, it is suggested that all patients exhibiting hypersensitivity to it should be desensitized. This is best accomplished by a method which employs a very small initial dose and which proceeds slowly as described.

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Suicidal Behavior in a General Hospital*

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THE number of suicides occurring in general hospitals throughout the country is not known with certainty. Tuckman and Lavell [*1*], in their study of 742 suicides in Philadelphia from 1951 through 1955, found that 4 per cent took place in hospitals. In a review of 37,860 admissions in a municipal general hospital from 1954 through 1957, Friedman and Cancellieri [*2*] reported three major suicidal attempts, two of which were successful. Levy and Southcombe [*3*] reported a suicide rate of thirty-eight per 10,000 admissions in a mental hospital. They stated that in 1945 the incidence of suicide in institutions was twenty-eight times higher than in the population at large, and that 20.7 per cent of the 14,782 suicides reported for that year took place in general or mental hospitals (18.8 per cent in general hospitals and 1.9 per cent in mental hospitals). They add, however, that most of the patients listed as suicides in general hospitals had made the attempt elsewhere and were taken to the hospital later. Friedman and Cancellieri [*2*], for example, noted that 272 patients who had made suicidal attempts elsewhere during the period 1945 through 1957 were admitted to the municipal hospital just mentioned. In 1949 there were 16,993 suicides in the United States [*4*]; of these, 3,495 were reported from institutions, 2,912 from general hospitals and 235 from mental hospitals. Again it should be noted that the place where death occurred was not necessarily the place where the suicidal act was performed.

In New York City [*5*] during 1956 there were 591 suicidal deaths; of these 140 were reported from hospitals, but not more than sixty-nine (11.7 per cent of the total number) resulted from self-destructive acts in hospitals. In the 140 deaths the method of suicide was as follows: barbiturate poisoning, thirty-three; other poisons, twenty; domestic gas, two; other gas, two; hanging, nineteen; drowning, one; firearms, nine; cutting and piercing, four; jumping, forty-seven; others, three. Turning to the sixty-nine patients who committed suicide in hospitals, 68 per cent jumped from windows; 27 per cent hanged themselves; and 5 per cent used cutting and piercing methods. Fifty-six of the suicides occurred in municipal or in voluntary hospitals; seven in state mental hospitals; three in Veterans Administration general hospitals; one in a home for the aged; one in a proprietary nursing home; and one in another hospital.

From 1947 through 1958, twenty-three patients committed suicide in the Bronx Veterans Administration Hospital, a general hospital in which less than 3 per cent of all admissions were women. (Table 1.) All the suicides were men; of these, two were Negroes. Sixteen were general ward patients (medical, surgical or neurological) and seven were psychiatric patients. During this time there were 110,000 hospital admissions comprising 103,400 general patients and 6,600 psychiatric patients. The psychiatric unit is an integral part of the hospital The suicide rate for all patients was 2.09 per 10,000 admissions; for the general patients it was 1.55 and for the psychiatric patients it was 10.6. There were 3.8 suicide deaths per 1,000 deaths. The hospital is a training center with university affiliations. Resident physicians are instructed in the importance of recognition of suicidal risks and of prompt request for psychiatric consultations. Patients suspected of harboring suicidal thoughts are transferred to the psychiatric unit.

Fourteen patients ended their lives by jumping from windows; two slashed themselves with razors (one cut his throat; the other, his wrists and arms); two patients committed suicide while on pass from the hospital (one by shooting; the other by drowning); one patient escaped from the hospital and threw himself under a train; two patients died in barbiturate coma; and two patients hanged themselves. The oldest patient was seventy-six years old, the youngest twenty-four. The duration of hospitalization varied from two days to 339 days. Sixteen patients had had previous admissions to the hospital. Of the entire

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TABLE 1

SUICIDES IN BRONX VETERANS ADMINISTRATION HOSPITAL 1947–1958

Case No.	Age	Race Religion Marital	Occupation	Days in Hospital	Diagnosis	Previous Suicidal Attempt	Psychiatric Consultation	Method of Suicide
1.	63	W,C,W	Ex-actor	259	Cancer of neck; tracheostomy; chronic pulmonary emphysema; arteriosclerotic heart disease	No	No	Cut throat and wrists
2.	64	N,P,M	Barber	121	Cancer of esophagus; gastrostomy; tracheostomy	No	No	Jumped from window
3.	39	W,H,S	Clerk	30	Hodgkin's disease with involvement of spine and collapse of vertebra	No	No	Cut wrists and arms
4.	64	W,H,M	Unemployed	46	Arteriosclerotic heart disease; congestive heart failure; diabetes mellitus; colostomy for cancer of rectum	No	No	Jumped from window
5.	76	W,P,W	Retired	40	Cancer of larynx with metastases to lung	No	No	Jumped from window
6.	40	W,H,M	Engineer	34	Melanoma with metastases to lung	No	No	Shot himself while AWOL
7.	30	W,C,M	Chauffeur	2	Rheumatic heart disease, class 3C (aortic and mitral disease)	No	No	Jumped from window
8.	61	W,C,M	Vegetable store proprietor	15	Arteriosclerotic heart disease; hypertensive encephalopathy; anginal syndrome; left hemiparesis	No	No	Jumped from window
9.	24	W,C,S	Student	141	Right hemiparesis secondary to congenital cerebral aneurysm	Yes	Yes	Drowned himself while on pass
10.	51	W,H,M	Social investigator	42	Chronic Parkinsonism	No	No	Jumped from window
11.	53	W,C,M	Station operator	5	Herniated nucleus pulposus; abscess of spine; neuralgia of lumbar spinal nerves; postsympathectomy	No	No	Jumped from window
12.	55	W,C,S	Unemployed	43	Cirrhosis of liver; esophageal varices; diabetes mellitus; cerebral arteriosclerosis with hemiparesis; senile cataract, postoperative	No	No	Jumped from window
13.	71	W,C,S	Unemployed	17	Postprostatectomy; reactive depression	No	Yes	Jumped from window
14.	68	W,C,M	Retired	158	Third degree burns of face and hands; plastic surgery	No	No	Jumped rom window
15.	46	N,P,M	Stock clerk	130	General paresis; optic atrophy (blindness); depression, hallucinations	No	Yes	Jumped from window
16.	32	W,C,S	Unemployed	339	Chronic osteomyelitis of femur; hyperthyroidism; chronic schizophrenia	No	Yes	Barbiturate coma
17.	30	W,P,S	Unemployed	9	Chronic schizophrenia, paranoid, with delusions	No	...	Jumped under train while AWOL
18.	28	W,H,S	Unemployed	240	Chronic schizophrenia, paranoid, with delusions	No	...	Hanging
19.	26	W,C,S	Laborer	7	Acute schizophrenia with severe anxiety and delusions	No	...	Jumped from window
20.	62	W,C,M	Cabinet maker	21	Involutional melancholia	No	...	Jumped from window
21.	37	W,C,S	Unemployed	22	Depressive reaction	No	...	Jumped from window
22.	28	W,C,S	Student	42	Chronic schizophrenia with depression	Yes (cut neck with razor)	...	Hanging
23.	24	W,P,S	Stock clerk	100	Severe psychopathy; heroin addiction; emotional instability	Yes (barbiturate overdose)	...	Barbiturate coma while AWOL

NOTE: Race: W = White; N = Negro. Religion: C = Catholic; P = Protestant; H = Hebrew. Marital status: M = Married; S = Single; W = Widower. AWOL = Absent without leave.

group, three had made previous suicidal attempts (two psychiatric patients and one general patient). With regard to religion, 58 per cent of the patients were Catholic; 17 per cent were Protestant; and 25 per cent were Jewish. The percentages for all admissions to the hospital were: Catholic 50 per cent, Protestant 35 per cent and Jewish 15 per cent.

The general ward patient who committed suicide was likely to be older and married; the psychiatric patient younger and single. All the general ward patients were chronically ill: Five had malignant neoplastic disease; six had chronic central nervous system syndromes; and three had advanced heart disease. One patient had been undergoing plastic surgery for disfiguring burn scars of the face and hands, and one patient who was an ambulatory schizophrenic had osteomyelitis and hyperthyroidism. Three patients (Cases 9, 10 and 16), originally admitted

to the general wards, were transferred to the psychiatric unit for treatment of mental symptoms and then returned to the general wards.

The suicide rate of the psychiatric patients was 6.8 times greater than that of the general ward patients. Three of the psychiatric patients who committed suicide were on locked wards. They were all delusional schizophrenics. One managed to run away and threw himself under a train. Another concealed 4-inch strips of cloth used for trouser belt-ties, made an improvised noose, and strangled himself by hanging from a door knob. The third patient, while being conducted to a laboratory for study, broke away from his attendants and plunged through a window. The remaining four psychiatric patients were being treated on open psychiatric wards at the time of suicide. All had been depressed but were responding to psychotherapy given by resident physicians under the supervision of psychiatrists. All four patients had participated in hospital activities and had had week-end passes.

A critical review of the clinical records indicates that in some patients the suicide may have been preceded by stressful or unusual circumstances; but in other cases nothing unusual was found.

CASE 1. A sixty-three year old widower, a former vaudeville actor, was admitted to the hospital for the twelfth time. For ten years he had required treatment of intermittent symptoms arising from pulmonary emphysema and arteriosclerotic and hypertensive heart disease. He was a friendly and outgoing person who would entertain his fellow patients with songs from his vaudeville act. On the eleventh admission metastatic cancer of the neck was discovered and a radical neck dissection was performed. A year later there was evidence of recurrence and he was readmitted. He was given x-ray treatments and a tracheotomy was performed. He had been in the hospital eight months when he was assigned to a new resident physician. Soon an antagonistic relationship developed. The patient thought he was being pushed out of the hospital and the doctor found the patient overdependent, uncooperative and untidy. A month later the patient was found dead in the bathtub. He had cut his throat and wrists with a razor. He left a note: "You can blame this on Dr. X who has examined me once since I became his patient four weeks ago. He took over when Dr. Y left and has been in this wing twice to see his other patients. This is not the hospital I knew under Dr. Z. I know that you will do something about this and other things that need changing. Ask Dr. A, Mr. B. and Mr. C. about me. They will tell you what a good job I done for morale of patients in the past. But I still maintain you should straighten out Dr. X so patients can get some treatment."

CASE 2. A sixty-four year old Negro barber was admitted with cancer of the esophagus. Treatment included gastrostomy, x-ray therapy and tracheotomy. Four months after admission he was interviewed by a social worker about going to a nursing home; his wife was ill and could not take care of him at home. He was worried about feeding and changing his tubes. The stomach feeding annoyed him; it was messy and ran down his legs. He had difficulty in speaking, could not swallow and had to expectorate every few minutes. It was necessary for him to communicate with the aid of paper and pencil. He asked, "Do you think I will ever get better than this?" The next morning he jumped out of a window.

CASE 3. A thirty-nine year old clerk was readmitted for further treatment of advanced Hodgkin's disease with invasion of the spine. There was collapse of the first and extensive involvement of the fifth and seventh thoracic vertebrae. He also had an infection of the urinary tract. Previous treatment included the administration of nitrogen mustard and x-ray therapy. One month after admission, at 3 A.M., he cut his arms and wrists with a razor. Before he died twelve hours later he told the psychiatrist that he tried to commit suicide because of pain and high fever.

CASE 4. A sixty-four year old former salesman was admitted for the sixth time for slowly progressive, remitting heart failure of nine years' duration. In addition to arteriosclerotic heart disease with auricular fibrillation he had diabetes mellitus and a colostomy which was established eight years previously after removal of a cancer of the rectum. He was highly unstable emotionally, being temper-ridden, impulsive and discontented. He was abusive to his wife who had supported him for ten years. As the symptoms of heart failure grew worse, he became more fault-finding, agitated and fearful of death. He was apprehensive of imminent diaster, spoke of dying, and wanted to go home to die. His mind became clouded with paranoid ideation. He thought the doctors and nurses were trying to poison him with narcotics. On the forty-sixth day of his hospitalization he persuaded his roommate to get him a glass of water, and while the room was empty jumped out of an open window.

CASE 9. A twenty-four year old student, three weeks before admission, had sustained right hemiparesis and motor aphasia as a result of hemorrhage from a cerebral aneurysm. In the hospital, carotid arteriography was performed but this was followed by aggravation of the hemiparesis. He became depressed and made a suicidal gesture by scratching his wrists. He was transferred to the psychiatric unit where in six weeks his depression gradually lifted and he was returned to the neurological ward. He participated in a rehabilitation program and seemed enthusiastic

about speech retraining. He made good progress and was permitted to have week-end passes. On one of these passes, 141 days after admission, he drowned himself.

CASE 13. A seventy-one year old bachelor was admitted to the hospital because of urinary retention resulting from an enlarged prostate. He was fearful of cancer, peevish, irritable, and uncertain about consenting to surgery. A psychiatric consultant noted that the patient was in good contact; orientation and memory were undisturbed; the patient said he was worried about cancer, but persistently denied suicidal thoughts. Ten days after admission a prostatectomy was performed. No malignancy was found. Postoperatively the patient did very well. He was prepared to live with his sister although he had always lived alone. The nurses' notes stated that he continued to be unstable and argumentative, and that he seemed depressed. He jumped out of the window on the seventh day after operation. On that day he appeared more cheerful, had joked with the nurses and other patients, and had eaten a hearty breakfast.

CASE 15. A forty-six year old married Negro was admitted to the eye ward because of failing vision. He was found to have general paresis with rapidly progressive, syphiltic optic atrophy. He developed paranoid trends, delusions of reference and taunting auditory hallucinations. He was treated with penicillin and malaria on a closed psychiatric ward. His mental condition improved but he became blind. He was returned to the medical service for further study and for training of the blind. On the 130th day of his hospitalization he got up at 2 A.M., groped his way to the bathroom, punched a hole in the window screen and jumped out. According to the record, he had been making progress in his retraining but never made a good adjustment to his blindness.

CASE 16. A thirty-two year old, single, post office worker was admitted to the orthopedic ward for treatment of chronic osteomyelitis of the femur. Later, he was found to have thyrotoxicosis and was transferred to the medical service. Psychiatric examination revealed that he had phobias, depression, deep-seated inadequacy, and some vague ideas of reference. A sister was a known schizophrenic and a brother also was mentally ill. The patient himself was fearful of becoming schizophrenic. He denied suicidal ideas. He was treated psychotherapeutically on an open ward, but had full privileges and was allowed regular week-end passes. Psychological tests showed that the world appeared threatening to the patient; he was fearful of women; intellectualization was a major defense. His diagnosis was chronic, mild schizophrenia. He was considered to be psychologically suitable for a thyroidectomy and he was transferred to the surgical service for preoperative preparation. Four days later, on the morning before the operation, he was found comatose in bed from an overdose of barbiturates which he had obtained outside the hospital. He never regained consciousness and died after being hospitalized for 339 days. The last note of the psychiatrist quotes the patient (in retrospect it seems like a suicidal statement), "I was told by my girl friend that something is missing; I feel no contact with people—this means I'll be going up for operation but it won't be a cure-all. There is a defect in my personality. I'm a 'Schiz' like my sister. I'm trying to face reality; the operation won't change things. I have no close friends."

CASE 20. A sixty-two year old Italian was admitted to the closed psychiatric ward for treatment of involutional melancholia. He complained of tiredness, backache and headache; he was agitated and depressed. He said, "Please do something to help me. I have pains in the stomach. I think I have cancer. When I swallow, I feel like I touch something inside of me." In two weeks he showed rapid improvement and was anxious to leave the hospital. He was transferred to an open ward but a week later, while sitting in the dormitory one afternoon with other patients, he suddenly leaped out the window, shouting "Please don't kill me."

CASE 21. A thirty-seven year old, single, unemployed man was admitted because of depression and alcoholism. He said, "I have no desire to do anything. I want to be alone and sit down in apathy. I get ashamed of my behavior, I can't stand it." He was treated psychotherapeutically on an open ward and did well. He never expressed suicidal ideas. He was always cooperative, rational and coherent, and was in excellent contact. His depression seemed to be lifting: he read, talked, and played cards with other patients. On the twentieth day of hospitalization the patient's mother telephoned the doctor to say that her son had told her that he was feeling much better and that he seemed to be in excellent spirits. The next day the patient jumped out the window.

CASE 22. A twenty-eight year old, single student was admitted to the locked psychiatric ward after an attempt at suicide by cutting his throat with a razor. His wound was slight; his depression lifted rapidly and he was sent to an open ward for continued psychotherapy. He seemed cheerful, and he ate and slept well. He went home on regular week-end passes. His psychological tests showed that he was unproductive, constricted and incapable of carrying out his ambitions. Diagnostically, he was considered to be a chronic, undifferentiated schizophrenic. He showed anxiety, helplessness and sexual doubts; he was unable to form mature relationships. On the forty-second day of his hospitalization he was found hanging beneath the stage of the recreation hall.

CASE 23. A twenty-four year old heroin addict was admitted to the medical service in deep coma.

He had taken 700 half-grain tablets of phenobarbital. He remained comatose for six days but finally responded to vigorous treatment. He had major character defects; his psychopathic behavior included lying, stealing, burglary, forgery, alcoholism, use of marihuana, barbiturates and narcotics. He was placed in a locked psychiatric ward where he regained some degree of emotional equilibrium, and later was sent to an open ward. He did fairly well for a few weeks but he remained emotionally unstable, impulsive and unpredictable. He was regarded as a serious suicidal risk. On the 100th day of hospitalization he ran away from the hospital, got drunk, stole a car, broke into a pharmacy and took a bottle of barbiturate capsules. He died in another hospital that same day of barbiturate coma.

Most of the general ward patients in this group may be classified as "rational" suicides. Since medical progress often leaves problems of old age and chronic disease in its wake, it is likely that the suicide rate in hospitals will increase. Of common occurrence were severe, chronic or terminal illness, multiple illnesses, pain, dyspnea, disfiguring operations and 'ostomies. Many of the subjects were past fifty years of age, lonely and hopeless, and in some instances helplessly dependent, both physically and financially. Such patients were often fearful of discharge from the hospital upon which they had placed their last desperate hopes. In some patients progress of the illness or other added threat to their security may have been responsible for panic reactions or acute depressions with or without paranoid features. Such patients (e.g., Case 1) are sensitive and may readily distort, exaggerate or misinterpret the behavior of hospital personnel as evidence of rejection [*6*]. Patients who are aware of the inevitably fatal termination of their illnesses need special attention and support; they may be unable to tolerate continued suffering and the prospect of certain death. Others who have always been self-reliant and resourceful find their helpless state unacceptable. They would rather die than be a burden. Some regard their misfortune as the final blow in a life of misery and failure.

Failing eyesight or fear of cancer may precipitate suicide. Deformities and surgical operations of the head, neck and face which distort the body image may overwhelm the narcissistic ego and precipitate acute depression [*7*]. Surgery in the aged often upsets the balance of previous high levels of emotional stability and integration, and depression frequently follows [*8*]. Central nervous system syndromes which permit the patient to retain a degree of understanding of the nature and extent of his incapacity but which deprive him of a full measure of inhibitory control may be responsible for a self-destructive act during a depressive episode.

One-third of all suicides occur in persons with frank mental illness, and suicide ranks high in the list of causes of death of the mentally ill. Those with depression, schizophrenia, psychopathy and central nervous system syndromes are to be regarded as potential suicidal risks.

In 1956 there were 6,055 general hospitals in the United States; of these, 976 reported facilities for the treatment of psychiatric patients [*9*]. With the establishment of more and more psychiatric units in general hospitals, and with the current trend away from locked psychiatric wards, it is to be expected that the number of suicides in general hospitals will increase. A high level of alertness and sensitiveness to the possibility of suicide will be required.

Turning to the general ward patients and the open ward psychiatric patients of this study, it is not known if the suicidal act was undertaken impulsively or after some deliberation and planning. Except for Cases 20 and 23, it was performed secretly and successfully, suggesting some consideration of a method of operation. Suicidal threats and gestures, if they occurred, were not recognized. In most cases the act was accomplished with violence and finality, perhaps signifying ultimate defiance and defeat. Why some patients apparently prefer to commit suicide away from the hospital, by running away or on pass, is not clear. One patient who harbored such intention intimated that he did not want to get the doctors in trouble. It is not uncommon for suicide to be preceded by a period of well being (Cases 13, 19 and 20). This is likely to occur in patients known to be depressed, and it emphasizes the oft repeated warning that the danger of suicide increases as the depression lifts. Occasionally, the self-destructive act is performed at the height of an episode of elation in the course of depressive illness. It seems as if the difficult decision to cast off all cares by ending one's life calls for a celebration.

ETIOLOGIC CONSIDERATIONS; PREVENTION OF SUICIDE

There is no easy formula which will serve to detect suicidal ideas or intention. Fifty per cent

of normal people are said to have fleeting thoughts of ending their lives [*10*]. It is well known that suicides may occur under the most diligent observation and care. There is the quiet, unobtrusive patient who executes an apparently carefully planned suicidal effort. There is the unpredictable, emotionally turbulent individual who takes his life under the pressure of some highly charged set of circumstances. Suicide is said to result "from a combination of forces from the individual's emotional make-up and from external stress [*11*]." It is a symptomatic act of finality, not a disease, and is therefore not listed in the Standard Nomenclature of Diseases.

The ultimate cause of suicide remains unknown. Psychoanalytic theories lay stress on deep seated, self-destructive drives which impel the person to destroy himself and at the same time commit intrapsychic murder of some introjected, authoritative figure, usually a parent or surrogate; or they emphasize the interaction of powerful, unconscious urges of aggression, submission and death wishes. Durkheim's [*12*] sociological theory attributed suicide to the departure of the individual from the "collective conscience" of his community; suicide results from faulty integration in the social group. Zilboorg [*13*] suggested that suicide is a type of developmental reaction which may appear as an outgrowth of any type of illness. He stated that most people who take their own lives are considered normal prior to the suicidal act; only after death are they assumed to have been depressed. Wahl [*14*] summarized another view, that suicide may be a magical act to achieve irrational, delusional or illusory ends. Rubenstein and co-workers [*15*] believe that attempted suicide is a desperate effort to change one's life. Moss and Hamilton [*16*] wrote that the death of one or both parents in early life is a frequent predisposing factor in suicide. The loss of the father particularly is said to foster death fantasies and to stir up self-destructive drives. It may be the result of emotional deprivation and the development of warped personalities; guiltladen, early sexual experiences, frequently incestuous or homosexual, are common.

A suicidal trend may be suspected, but suicide cannot infallibly be predicted. If we transfer a patient to a locked ward to guard against suicide, we cannot be sure that he would have made an attempt had he not been transferred. Friel and Frank [*17*] suggest that indicators of potential suicide occur in 40 per cent of those who attempt suicide. These indicators include preoccupation with accounts of suicide and death, unduly vigorous denial of suicidal intention, change in personality with depression, careless personal hygiene and a history of previous suicidal attempt. Hertz [*18*] studied the psychological test records of 113 clinically suicidal patients. She listed ten "suicidal" configurations in the Rorschach records of these patients and stated that the appearance of six or more of these configurations was reliably indicative of suicidal trends. The elements in her configurations are depression, active psychological conflict, suicidal ideation, deep anxiety, neurotic involvement, withdrawal, constriction, sudden emotional outburst, resignation and agitation. Jamieson and Wall [*19*] in their study of suicide in hospitalized psychiatric patients emphasized depression, guilt, self-depreciation and self-accusation, agitation, hypochondriasis, insomnia, fear of losing control and hurting others, suicidal preoccupations, attempts at suicide and suicidal talk. Robins and co-workers [*20*] report that in 69 per cent of 134 consecutive cases of suicide the patients communicated their suicidal ideas and 41 per cent made a specific statement of intent to commit suicide. Vail [*21*] finds that physicians are not always alert to various suicidal warnings given by patients with depression, character disorders or addiction to alcohol.

In his analysis of eleven suicides in a Veterans Administration general hospital during a five-year period, Pollack [*22*] emphasized the relation of suicide hazard to organic psychosis. His typical case was a chronically ill, elderly man (often with a history of alcoholism), beset with social problems and subject to episodes of confusion. In ten of his cases, suicide occurred by jumping from a window at night after a day or two of emotional disturbance. The brief and perhaps mild psychotic manifestations had escaped the attention of the staff.

In our group of twenty-three patient, 61 per cent met death by leaping from windows. Surely a number of lives could be saved by guarding the windows of hospitals against hazardous opening by patients.

HOSPITAL REACTION TO SUICIDE

Certainly no physician can regard the suicide of his patient with indifference. Guilt feelings may reproach him, and he may be stirred by anger at himself and at the patient. Sometimes the physician experiences the equivalent of a

mourning reaction, marked by humiliation, irritability, self-criticism and lowered self-esteem. There may be uneasy feelings that he has incurred the resentment of his superiors and the hatred of the patient's relatives.

A suicide in a hospital sets up waves of disturbances. Patients are uneasy and restless. Suicidal thoughts may be aroused in the more chronically ill. Some are frightened lest the doctors be incapable of coping with patients' impulsive and uncontrollable self-destructive urges. Nurses are apprehensive of any unusual patient behavior. Resident physicians are reminded of precautions against suicide. Administrative authorities are concerned with the possibility of lawsuits. This state of alarm, however, gradually subsides in a week or two, and conditions return to normal.

TYPES OF SUICIDAL BEHAVIOR IN A HOSPITAL

A variety of suicidal behavior occurs in a hospital. There are individuals who might be considered chronic suicides; for example, the patient with severe diabetes who disregards his prescribed diet, or the patient with peptic ulcer who drinks and smokes excessively. There are patients such as those with advanced tuberculosis whose very lives depend upon continued hospital treatment, but who nevertheless insist upon leaving the hospital. When relatives join forces with such a patient, they become parties to an act which hastens death. Most difficult of all to deal with are the nearest of kin who override all medical advice and are obdurate in their demands for the release of patients known to be depressed and possibly suicidal. A militant older sister, for example, obtained the release of a brother against urgent medical advice. She ridiculed warnings of suicide; she had always taken care of her brother and would continue to do so. The next day he jumped in front of a train and was killed. Meerloo [*23*] calls such circumstances psychic homicide. He regards suicide in such cases as a supreme masochistic act to escape domination of a hostile person. It is the culmination of a struggle of unconscious hostile forces between two psychically linked individuals, in which the stronger ego overcomes the weaker ego. The weaker person destroys himself but in doing so also kills his enemy in fantasy. Finally, there is a group of people for whom chronic illness satisfies deep-seated demands for dependency. For them good health is threatening since it imposes responsibilities beyond their tolerance; it may precipitate panic, depression and self-destruction. We have observed three patients in whom acute psychotic reactions developed after mitral commissurotomy for relief of chronic rheumatic heart disease; one patient died.

BARBITURATES, SLEEP AND ACCIDENTAL SUICIDES

Many patients attach great importance to sleep. Loss of sleep means irreparable physical decline. To insure sleep they may hoard barbiturates which are commonly prescribed by physicians. The drugs are obtained from various sources: from other patients, from outside druggists and physicians, from friends and relatives, from the black market. Samples of barbiturates may be stolen from doctors' offices. One patient returned a post card requesting the drug company to send him a further supply of barbiturates! Not uncommonly, an excessive dose may fail to induce sleep. The thoroughly drugged, half-delirious patient may continue to take pills or capsules automatically until he becomes comatose. Fatal cases are listed as suicides although there may have been no suicidal intention. They just wanted to sleep.

RAPPORT BETWEEN DOCTOR AND PATIENT

It seems clear that the more the physician knows about his patient, the more he will be able to arrive at an estimate of the suicidal potential of that patient. If the doctor has the interest and takes the time, he will discover that many patients have what they regard as insurmountable problems; that many react to the illness with undue apprehension, and indeed regard the illness itself as punishment for past transgression. If the doctor has sufficient interest, he will acquire a fund of knowledge of the patient's attitudes about life, of his prevailing mood, and of his prospects for the future. Sympathy, tact and understanding are necessary. Blunt questioning may evoke denials of suicidal preoccupation; on the other hand, in some patients a seductive or overfriendly approach may be threatening and panic producing. The emotional bond between doctor and patient is a powerful therapeutic influence. Proper and constructive use of this bond may make the difference between the patient's wanting to live or to die. Neglect, rejection, thoughtless remarks, indifference, a "brush off" could be important in precipitating a suicidal act.

In this age of specialization and laboratory

medicine the patient as a whole may be forgotten. All physicians should be familiar with the symptoms of depression. Not only is there pathological lowness of mood; there may also be agitation, feelings of guilt, hypochondriasis and preoccupation with minor physical symptoms. Sometimes monosymptomatic fixation occurs. The patient is abnormally quiet and subdued; he does not participate in social activities; he sits and broods; looks older and downcast. He may show increased religious sentiment. Constipation, insomnia and diminished sex drive are common. It is important to remember that patients can conceal depression. They may rise to an occasion and present a falsely cheerful aspect. Sometimes a depressed person will successfully mask his symptoms for weeks or months, performing his work and giving the impression of being normal. When alone, such people quickly lose interest in the environment and sink into a state of apathy.

To suspect suicide is to prevent it, but the suspicion should be based upon fine clinical judgment. Many suicidal statements are idle remarks; not all depressed patients are suicidal. Not all patients with central nervous system syndromes are suicidal risks; not all schizophrenics need be in psychiatric wards. Certainly not all terminally ill or seriously ill patients should be sent to locked wards. The decisive 'x' factor [*24*] which impels a patient to take his own life is not known, but the deeper the rapport with the patient and the greater the knowledge of the patient, the better able will the sensitive physician be to assess the suicidal hazard.

SUMMARY

In an eleven-year period twenty-three patients committed suicide in a general hospital with psychiatric facilities, admitting almost exclusively male patients. Of the twenty-three suicides, sixteen were general ward patients, seven were psychiatric patients. The hospital suicide rate was 2.09 per 10,000 patients; for the general ward patients it was 1.55, for the psychiatric patients it was 10.6. In 61 per cent of the cases death occurred by jumping from windows.

Typically, the general ward patient was chronically or terminally ill with malignancy, heart disease, central nervous system syndrome or other neurological disease, or a condition which was disfiguring or involved loss of sight. Multiple illnesses were common. Predisposing factors included social difficulties and an overwhelming sense of helplessness and uselessness.

Three of the seven suicides in psychiatric patients occurred in delusional schizophrenics. The remaining four had depressive symptoms which appeared to be responding to psychotherapy. In two psychiatric patients and one general ward patient, suicide was preceded by a period of well being.

Etiologic theories and indications of suicide are mentioned; various types of suicidal behavior in a hospital are discussed; and suggestions are made for the prevention of suicide. The importance of sensitiveness to the possibility of suicide and of good doctor–patient relationships is stressed.

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Reviews

The Long Term Management of Hepatolenticular Degeneration (Wilson's Disease)*

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One year after S. A. K. Wilson [*1*] first described the disease which is now known by his name, Rumpel [*2*] reported that an unusually large amount of copper was present in the liver of a patient dying of the disease. Subsequently, particularly in the past decade, evidence has accumulated which has led most investigators to believe that Wilson's disease is a syndrome which represents the end results of an hereditary defect in copper metabolism [*3–16*]. The inter-relationships of the various disturbances in the metabolism of copper present in these patients are not yet clearly defined. Nevertheless, rational therapy and prophylaxis have been based on a simple, partly hypothetical, summary of the pathogenesis of the disease which may be stated thus: subjects in whom Wilson's disease develops have inordinately high concentrations of copper in many organs and tissues because they seem to be unable to limit the absorption of dietary copper, or to excrete copper already absorbed, or do both, in the same manner as normal subjects. The excessive copper content of the body which results appears to bring about the histologic and physiologic damage to many structures which constitutes the disease.

The symptoms and clinical and biochemical signs of Wilson's disease may develop gradually or suddenly, and they do not appear in the same sequence in all patients. Apparently the first detectable abnormality is the hereditary deficiency or absence of the plasma copper-protein, ceruloplasmin [*7,9,10,17*], the relationship of which to the other manifestations of the disease is obscure. Perhaps an equally early sign is an elevation of the concentration of non-ceruloplasmin plasma copper [*10*] and of copper in the liver [*58*]. Only later do the copper deposits seem to be toxic to the liver, brain and kidney, and other manifestations of the illness appear, such as corneal Kayser-Fleischer rings [*18*], ungual azure lunulas [*19*] and bony changes [*20,21,83*]. It is rare for any of these to appear before the age of about eight years, after which the disease may progress so rapidly that death by the age of ten or eleven may occur. The illness develops in the second or third decade although some patients survive into the fourth or fifth decade [*6*].

The present paper describes a therapeutic and prophylactic regimen, based on this concept of the pathogenesis of Wilson's disease, and the results of this treatment as observed in six subjects over a period of three to five years. The aims of treatment were twofold: (1) to minimize the dietary absorption of copper and (2) to promote the excretion of copper already absorbed. Much of the published data indicate that there are several ways to achieve both of these goals. Theoretical considerations of how to achieve the first have led to copper-poor diets, combined with cation-exchange resins [*8,11*] or potassium

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sulfide [*9,10,40*] to precipitate whatever copper is in the food; for the second, various workers have used the parenteral administration of 2,3-dimercaptopropanol (BAL) [*5–13*], ethylenediaminetetraacetic acid (Versene®) [*7–12,30,46*], and amino acids [*9,10,50,51*], and the oral administration of β,β-dimethyl cysteine (penicillamine) [*13,41,46,47,54*], and these have all proved to be of value. In addition, empirical use of adrenal steroids and ACTH has increased cupriuria in a few patients [*11,30,36,57*]. As will be apparent from our case reports, we have made use of several of these various types of therapy as they were made available during the course of our study.

The results of our efforts have not been startling, and they have been difficult to assess largely because of the spontaneous exacerbations and remissions which characterize Wilson's disease [*41*]. Nevertheless, we believe, our observations indicate that removal of copper from these patients produces amelioration of symptoms and signs of the disease. More important, perhaps, is the implication in these results that early treatment of infants who are diagnosed as having asymptomatic Wilson's disease may delay or even prevent the manifestations of the illness when they would otherwise probably develop.

METHODS

Ceruloplasmin. Determinations were made by measuring the oxidase activity of serum toward paraphenylenediamine, as previously described [*16*].

Copper. Quantitative determinations of copper in serum and in urine were made by a method in which wet ashing with perchloric and sulfuric acids is followed by neutralization and color development with dicyclohexanone oxalyldihydrazone. Color intensity is measured in a spectrophotometer. With material containing 1 μg. of copper this method has an accuracy of about 2 per cent.*

CASE REPORTS

CASE 1. D. S. was a twenty-one year old unmarried woman when she was admitted to the Columbia-Presbyterian Medical Center in 1954. She had noted for six years that she bruised easily and there were frequent epistaxes. In the preceding year or two increased irritability, some clumsiness, an unsteady and smaller handwriting and some slurring of speech had appeared.

Her past history revealed no abnormalities. Her mother, of Irish descent, was forty-six years of age in 1954 and in good health. Her father, of German descent, was fifty years old in 1954, and also in good health. The patient has two brothers, one two years older, and the other ten years younger than she, both of whom are healthy. There are no dead siblings.

In 1954 the patient appeared mildly pale, with a somewhat retracted upper lip. There were slight, intermittent resting tremors of her hands. Deep tendon reflexes were very active. She walked well despite a moderate dorsal kyphosis. There were bilateral Kayser-Fleischer crescents at the superior and inferior corneal margins. No spider angiomas were seen. Examination of the abdomen was unsatisfactory because of rigidity. Laboratory data included absence of detectable serum ceruloplasmin. Other results are given in Table 1. Roentgenographic examination of the abdomen revealed a small liver and considerable enlargement of the spleen.

Soon after discharge drooling appeared, the tremors increased in severity and some cogwheel rigidity of the upper extremities was noted. In April 1955 the patient experienced the first of several episodes of abdominal pain, associated with nausea, for which she was hospitalized. This lasted for five days and subsided spontaneously. No cause for the pain could be found. Numerous ventricular premature contractions were first noted, incidentally, during this hospitalization. During the succeeding three years about ten episodes of similar abdominal pain recurred and despite extensive clinical and roentgenographic examinations, they remained unexplained. Rather frequent bilateral, needle-like headaches appeared in June 1955.

For about a year and a half she was treated by means of a low copper diet and two tablespoons of carboxylic cation exchange resin (Carbo-Resin®) with each meal. Nevertheless, the neurological symptoms and signs described gradually but definitely became worse and moderate adiadochokinesia appeared. In September 1956 she was given five intramuscular injections each of 1.5 cc. 10 per cent BAL. She complained of dizziness without true vertigo on the days BAL was given. The administration of BAL was stopped, following which the patient felt very weak, could not walk without help, and was almost unable to talk or raise her left arm. She also had transitory pain in the left upper quadrant of the abdomen, the relationship of which to BAL was obscure. In October 1956 a small hematemesis followed an episode of vomiting, and esophageal varices were demonstrated by means of a barium swallow. By January 1957 the patient was unable to unbutton her sweater, her handwriting had deteriorated (Fig. 1), there was violent resting tremor of both hands, and intentional movements were almost impossible. Her walking seemed stiffer. She was open-mouthed but did not drool much. Abdominal pains were present but were much less troublesome than the neurologic difficulties. On examination, the knee and

* Complete details of this method, in mimeographed form, can be obtained on request to the authors.

TABLE I

LABORATORY DATA

Data	Case I (D. S.)			Case II (G. G.)			Case III (D. W.)			Case IV (R. P.)				Case V (J. B.)			Case VI (W. G.)		
	1955	Range During Therapy	1958 1959*	1954	Range During Therapy	1958 1959*	1955	Range During Therapy	1959	1954	Range During Pregnancy	Range During Therapy	1959	1956	Range During Therapy	1958 1959*	1955	Range During Therapy	1958 1959*
Ceruloplasmin (mg. %)	<1	<1	<1	<1	<1	<1	<1	.....	0	7.0	13.8–19.0	7.4–7.8	6.7	<1	<1	<1	<1	.....	<1
Serum copper (μg. %)	.....	16.5–74	.....	.....	8.5–23.0	74.5	33.0	18.2	14	.....	70.5–155	55.4	51	.....	.....	26	.....	.....	.....
Hemoglobin (gm. %)	9.0	8.7–13.8	14.0*	13.0	9.8–12.0	12.0*	10.3	9.0–12.9	11.8	12.0	10–11.2	9.2–12.9	13.2	13.0	12.2–15.4	15.6*	10.9	12.3–14.4	12.6
White blood cells (per cu. mm.)	3,350	2,450–5,700	5,000*	3,850	950–4,900	1,800	6,700	1,500–4,900	2,400	5,100	5,700–10,000	1,400–10,600	1,800	7,200	2,400–7,300	4,550*	4,850	5,900–11,900	8,600
Platelets (per cu. mm.)	36,000	14,000–100,000	46,000*	54,000	20,000–60,000	56,000*	95,000	24,000–176,000	75.0	Normal	50,000–62,000	18,000–74,000	54,000	.....	4,000–48,000	72,000*	354,000	86,000–555,000	208,000
Bilirubin (mg. %)	0.7	0.88–1.1	1.2	.....	0.45–1.1	0.33	.....	0.51	0.66	0.2	0.7–9.0	1.0	1.84	.....	0.33–0.52	.....	0.4	.....	.21
Bromsulphalein, % retention at 45 minutes (5 mg./kg.)	.....	8.5–50	30	6	0	5	18 (30 min.)	6–7	8.2	18 (30 min.)	.....	26.5	.....	.....	.....	.....	0	1	1.4
Cephalin flocculation (1–4+)	3	3–4	4	0	3	2	2	3	1+	3+	3+–4+	4+	4+	.....	0	Trace	.....	0	0
Thymol turbidity (Maclagan units)	3	6.0–10.7	4.8	0	0.7–3.1	0.4	3	1.1–1.5	.55	3+	10.7–22.4	10.9–15.9	12.3	.....	1.1	0.75	.....	Negative	.40
Serum protein (gm. %)	6.3	6.1–6.6	6.0	7.6	6.6	6.6	7.0	5.4–5.85	6.2	6.8	6.8–7.3	6.4–7.0	6.9	6.8	6.6–7.0	7.1	7.9	.....	7.5
Albumin (gm. %)	3.6	2.1–3.2	3.1	5.3	3.6	3.8	3.8	4.0–4.3	3.6	3.9	2.5–3.8	3.0–3.2	2.7	4.6	3.7–5.1	5.0	5.5	.....	5.2
Alkaline phosphatase (Bodansky units)	4.4	2.3–3.6	4.9	5.5	1.6–2.1	4.6	.....	4.9–6.9	8.4	4.7	2.3–18.9	3.9–6.5	7.4	1.7	1.4–1.8	3.4	.....	8.2	8.5
Prothrombin time (seconds)	18	18.6–24.8	.....	16	18.8	18.5*	15.0	16.0–21.0	22.6	4	.....	16.0	17.4	.....	.....	14.0	.....	20.0	.....
Serum cholesterol (mg. %)	218	100	120	.....	154–208	140	.....	150–172	100	494	180–259	220	240	.....	137	.....	256	0	200
Cholesterol esters (mg. %)	.....	60	90	.....	116–130	115	.....	119	80	296	110–186	.....	140	.....	98	.....	179	.....	160
Uric acid (mg. %)	.....	2.4	.....	.....	2.0	3.5	.....	4.5	.....	.....	3.2	4.75–7.4	.....	.....	.....	4.6	.....	.....	.....
Urinary α-amino N (mg. per 24 hr.)	.....	447	.....	.....	236	.....	.....	735	.....	.....	.....	195	.....	.....	275	.....	.....	127	.....

* Data obtained in 1959.

ankle jerks were hyperactive, the former being almost tetanic. Unsustained clonus could be elicited in the ankles. There were several spider angiomas on the arms. The abdomen was so rigid that neither liver nor spleen could be felt, but the area of splenic dullness appeared enlarged to percussion.

The low copper diet and resin were continued, and penicillamine therapy was added to the regimen in February 1957. By May only subjective improvement was noted. During the summer of 1957 a slight, nonpruritic, erythematous eruption, with a few white-topped papules, appeared over the face. This regimen has been continued, essentially without interruption, to the present (April 1959).

The patient now has really no complaints. She is stoop-shouldered, walks well with some associated movements, shows only slight tremor of the outstretched arms and performs the finger-to-nose test well. (Fig. 1.) Adiadochokinesia is slight. Knee jerks are sustained in tetanic fashion and the ankle jerks are extremely brisk. The mouth is generally open but speech is clear. Virtually no Kayser-Fleischer rings or crescents can be seen on slit-lamp examination. Multiple extrasystoles are still present. The spleen is palpable, but the liver edge cannot be felt, and the extent of liver dullness seems less than normal.


Dorothy ... Marie Seb
Dorothy Anne Mens -Sis
1-16-57

3
April 21, 1959

Dear.

How's ? I am feelin fine and am behaving myself as best as I can. I am also taking my medicin and sticking to my diet.

My Aunt is doing nicely and we expect her home Wednesday or

FIG. 1. Case I. Two specimens of handwriting.

CASE II. G. G. was a thirteen year old girl when admitted to the Neurological Institute of the Columbia-Presbyterian Medical Center in September 1954. She had been well until the age of twelve, when her mother noted that she began to talk as though she "had marbles in her mouth." Within about six months she was noted to be "nervous," "unable to sit still," and "shooting her arm out suddenly when talking." Her gait became affected, and in August 1954 she had an episode of almost complete paralysis and aphasia, from which she recovered spontaneously.

Except for the usual childhood diseases, frequent epistaxes and "virus pneumonia" in 1950, she had been healthy. She had received penicillin for various infections.

In 1954 her mother, of Scandinavian and English descent, was thirty-eight years old and her father, of French extraction, was fifty-four years old. Both were healthy, as were two sisters, aged eighteen and ten years, and a brother, aged ten months. There were no dead siblings.

Physical examination showed the patient to be a thin, active, cheerful young girl. Her upper lip was slightly retracted revealing her front upper teeth. There was a moderate amount of drooling, and an open-mouthed expression. She was able to walk well, but there was impairment of associated movement of the left arm. Her speech was barely understandable. There was intermittent twitching of the outstretched fingers and cogwheel rigidity of the left arm. There were bilateral Kayser-Fleischer rings which were easily visible without a slit-lamp examination. A sharp and firm liver edge was felt 3 fingerbreadths below the costal margin, but the spleen was not palpable. Laboratory investigations revealed a plasma ceruloplasmin level too low to be determined quantitatively. Other results are shown in Table I. Roentgenograms of the skull and chest revealed no abnormalities, and a barium swallow disclosed no esophageal varices. Intelligence testing revealed an I.Q. of 95 with only slight inconsistencies suggestive of cerebral malfunction.

On her discharge from the hospital a low copper diet and two tablespoonfuls of Carbo-Resin® with each meal were prescribed.

Through early 1955 the patient became steadily and definitely worse with respect to talking, walking and drooling. Marked plastic and cogwheel rigidity was found on examination of her arms. By April her speech was virtually unintelligible, and she could not write without the greatest difficulty. Her mental state was extremely labile and she occasionally exhibited shrieking tantrums. She would rapidly turn from laughing to crying, during which her mouth was widely open and she seemed almost unable to sob. She would emit a high-pitched, constant whine with saliva and mucus streaming from her mouth and nose. Her outstretched hands were kept in flexion, particularly on the left. The liver was palpable and splenic dullness was increased but there were no other signs of hepatic dysfunction.

In the spring of 1955, treatment with 10 per cent

BAL was instituted at a dosage of 1 cc. given intramuscularly six times weekly. The administration of resin was continued. By the end of May she had been given approximately 37 cc. of BAL, during which period vomiting, occipital headaches and dizziness were prominent. In addition, all of the symptoms which had preceded treatment became so much worse that BAL was discontinued. Within a month there was marked improvement. She could walk and speak, although it was difficult to understand her. She was even able to write, which had been impossible a month before. In another month, after 8 cc. of BAL was cautiously given, she was alert, cheerful, drooling very little, and talking with remarkable clarity. With only diet and resin therapy, and no further administration of BAL, by October 1955, she could do almost everything except comb her hair. But she still spoke poorly, and there was considerable drooling. Her spleen was now palpable. The administration of BAL was reinstituted and she received 25 cc. from October through December 1955. In January 1956 she became very tired and extremely pale, with a hemoglobin of 4 gm. per cent and indices characteristic of iron-deficiency anemia. BAL and resin therapy were interrupted and she responded well to ferrous sulfate, her hemoglobin rising rapidly to over 10 gm. per cent.

In March 1956, roentgenographic studies revealed esophageal varices for the first time.

Resin therapy was begun again without the administration of BAL in April 1956. By November she was going to school regularly and, except for some fatigue, she managed well. Her behavior had quieted down considerably. Neurologic examination showed a well performed finger-to-nose test, no tremor of the outstretched hands, although the fingers were hyperextended, and moderate adiadochokinesia. There was no rigidity of the arms. Kayser-Fleischer rings, and liver and spleen were unchanged.

In December 1956 penicillamine therapy was begun, in a dosage of 1 gm. daily; five days later her temperature rose to 105°F.; she had a cough, and a generalized erythematous, pruritic eruption developed. All three subsided when drug therapy was discontinued. Two weeks later, within six hours after being given only 0.25 gm. penicillamine, preceded by 7.5 mg. prednisone, she had a temperature of 101°F., a red, sore throat, with swollen lymph nodes and an erythematous eruption on her face which spread over her entire body. These too subsided within two days. Together with 20 mg. prednisone given daily (which was discontinued uneventfully in August 1957) penicillamine treatment was finally instituted successfully in March 1957. From April through August she was given between 1 and 2 gm. of penicillamine daily, except for an eight-day interval. In August a fine, papular, non-erythematous eruption was seen on her chin and forehead. Penicillamine therapy, interrupted in August, was begun again in September 1957, and continued, together with administration of resin, to the present. She is now (April 1959) little incapacitated by her disease. Its most notable effect is in her speech; she talks rapidly with words tumbling out one over the other, so that it is not easy to understand her. She has no disability in her hands. Her gait, although somewhat awkward, is still within normal limits. The previously visible Kayser-Fleischer rings have faded and only faint residues can be identified on slit-lamp examination. She is attending school regularly.

Case III. D. W. was eleven years old when first seen in February 1955. He complained of headaches and abdominal pains of six months' duration. The latter were chiefly in the right upper quadrant, occurred several times a week and lasted for a few hours at most. The headaches were frontal, dull, occasionally accompanied by nausea and vomiting, and occurred about twice weekly. There were no neurologic complaints or other symptoms. His past history revealed no abnormalities except for the fact that he had been quite obese until the onset of his abdominal pains, when he had lost weight.

His mother and father, both of Irish descent, were unrelated and were healthy, the mother forty-three and the father forty-seven years of age in 1955. A brother, eight years older than the patient, had died of Wilson's disease at fifteen years of age. A sister, seven years older than the patient, was alive and well.

Physical examination revealed a large, cooperative, freckle-faced boy of eleven who looked normal. Neurologic examination revealed no abnormalities. Slit-lamp examination revealed minimal but definite bilateral Kayser-Fleischer rings. A firm, tender liver was palpated 4 cm. below the right costal margin. A moderately enlarged, hard and non-tender spleen was felt 7 cm. below the left costal margin. There were multiple small and large ecchymoses. Laboratory examination revealed absence of plasma ceruloplasmin and a total serum copper of 33 μg. per cent. Other results are given in Table I. The diagnosis of Wilson's disease having been established, a low copper diet and two tablespoonfuls of Carbo-Resin with each meal were prescribed.

In June 1955 no esophageal varices could be demonstrated by roentgenographic studies. Throughout the summer of 1955 he was able to play baseball and swim well. By the fall of 1955 he had gained 15 pounds and had had recurrence of headaches and abdominal pain when the resin therapy was stopped for about three weeks. There were no significant changes in his general physical and neurological examinations. A course of 14 injections of 1 cc. 10 per cent BAL was administered intramuscularly. In January 1956 the abdominal pain returned and, for the first time, some slight, coarse tremors of the fingers of the outstretched hands were noted. A second course of BAL had to be interrupted after the ninth injec-

tion, because the patient refused to take any more. The diet and administration of resin were continued. By August 1956 obvious neurologic symptoms had developed; his right hand was held rigidly at times, his mouth was almost always open, he drooled considerably and his speech was slurred. There was some dragging of the right foot on walking. His outstretched hands showed a fine resting tremor, more prominent on the right, and intention tremors were also apparent. Finger-to-nose test was performed well, but there was moderate adiadochokinesia. Furthermore, he had become almost unmanageable at home, behaving savagely when frustrated.

In January 1957 the patient was given penicillamine regularly, although occasional episodes of leukopenia have necessitated temporary interruptions in its administration. Nevertheless, by May 1957 his neurologic symptoms and signs were worse; he had difficulty drinking out of a glass without a straw, could not lace his shoes, and was noticeably slow in dressing. His speech was indistinct and he was barely able to write. Adiadochokinesia was marked. He tended to hold his right arm rigidly behind his back, with the right thumb flexed firmly in the palm. There were frequent wide, paroxysmal flapping movements of the right arm. Kayser-Fleischer rings were visible by slit-lamp examination. In June and again in August 1957 a papular, scaly, flaking eruption developed on the arms, legs and abdomen, but this promptly subsided following institution of 20 mg. of prednisone daily for one week. In August an anemia (hemoglobin, 9.6 gm. per cent) was noted which responded promptly to ferrous sulfate. Several subsequent recurrences of anemia required reinstitution of iron.

By July 1958 a slight improvement in his neurologic status could be noted. The right arm still was held somewhat stiffly and occasionally seemed to swing out of control. Intention tremor was present. However, the outstretched fingers showed no tremor and finger-to-nose testing was performed quite well. Adiadochokinesia, particularly on the right, was still present. There was no drooling. No definite Kayser-Fleischer rings could be seen on slit-lamp examination. The liver was not enlarged but the firm, non-tender spleen now filled the entire left upper quadrant of the abdomen. The superficial veins of the trunk were prominent. Around the trunk there was a non-pruritic, non-erythematous, scaling eruption of the skin.

Penicillamine therapy has been continued to the present (April 1959) and his condition has shown steady, if slow, further improvement. The intention tremor, the stiff right arm and wild swinging movements are no longer present. The spleen, however, has continued to become progressively enlarged.

CASE IV. R. P., a single, female bookkeeper, was first seen in 1954 at the age of twenty-eight years, complaining of tremors. In 1942 this patient had been hospitalized with what appeared to have been an acute attack of hemolytic anemia. In 1953 she noticed the gradual onset of intention tremor of her hands. Within a year the tremors had progressed to involve her feet, head and abdominal muscles. They were generally aggravated by emotional upsets.

Since the age of six she was known to have had xanthelasma and xanthomata tendinosa over the extensor surfaces of the knees, elbows and Achilles' tendons.

The patient is the daughter of a Jewish mother and a German father. The mother required temporary confinement in a mental institution at fifty-five years of age but had no neurologic disease. One sister, who is seven years older, was living and well. A cousin was said to have died of a "liver tumor" at the age of twenty-five.

On physical examination, there was retraction of the upper lip with some exposure of the upper teeth without drooling. A coarse resting and intention tremor of her hands, and an inconstant head tremor were noted. Finger-to-nose test was impaired on the right with only slight difficulty apparent on the left. There was no rigidity. Bilateral Kayser-Fleischer rings were prominent. Several spider angiomas were present on the upper arms and a number of ecchymoses were noted on her legs. Non-tender hepatomegaly and splenomegaly were present. Laboratory investigation disclosed a plasma ceruloplasmin of 7 mg. per cent. The serum total lipids were 2,107 mg. per cent (the serum was grossly lipemic), and phosphatides were 426 mg. per cent. Other results are given in Table 1. Cholecystography showed a poorly functioning gallbladder containing at least eight radiopaque calculi. Roentgenographic examination of the chest showed bilateral cervical ribs. Studies with barium revealed no esophageal varices.

In addition to Wilson's disease she was thought to have essential hyperlipemia, and chronic cholecystitis and cholelithiasis. Consequently, both a low copper and a low fat diet, as well as Carbo-Resin were prescribed. Nine courses of BAL totaling 154 cc. of 10 per cent solution were administered between December 1954 and August 1956. Almost every one of these courses caused a temporary worsening of her neurologic symptoms, and some of the injections were followed by nausea, vomiting, cramps in her legs, severe headaches and painful lumps in the buttocks. Nevertheless, between courses a progressive improvement in tremors occurred. Two months after the last course of BAL her outstretched hands showed almost no tremor, although there was marked intention tremor of her left arm. The head was almost free of tremors.

In February 1957, three months after her marriage, an exacerbation of the manifestations of Wilson's disease occurred. Her left hand was almost useless for fine actions, a less intense tremor was noticeable on the right. Tremors of her head had become more violent. Penicillamine therapy was first instituted at



FIG. 2. Case IV. Two specimens of handwriting.

that time. For two weeks she received 1 gm. per day, and this caused some nausea. Initially there was considerable worsening of her tremors, as there had been with BAL therapy, so that by March she was unable to pick up a glass at all, and her right hand trembled so much that she had to hold it with her left in lifting food to her mouth. Nevertheless, as was also noted with BAL, following the course of penicillamine she improved considerably as compared with her condition prior to treatment. The administration of penicillamine was reinstituted in June 1957, in a dose of 1 gm. per day, and was continued until August, when it was thought advisable to stop it since the patient was in her third month of pregnancy. There was no great change in her neurological status during her pregnancy, despite the lack of specific therapy for Wilson's disease. In the third trimester her xanthelasma and xanthomas disappeared, the number of spider angiomas increased considerably, and she became very irritable. In this trimester her serum ceruloplasmin concentration rose to 19 mg. per 100 ml., a finding which has been noted previously in another patient [*79*], as well as in normal women [*80,81*], and which may be related to the effects of estrogen on ceruloplasmin concentration [*41,82*]. In the six weeks before delivery there was excessive weight gain, headache and marked jaundice with a serum bilirubin of 9 mg. per cent of which 4.5 was direct-reacting. Nevertheless, she delivered a healthy boy. Postpartum there was progressive decrease in the intensity of her jaundice, but ascites and ankle edema appeared and persisted for eight weeks. By the middle of February 1958, two weeks after her delivery, she was essentially in the state she had been in before pregnancy except for fluid retention. Administration of penicillamine was begun again, at first in a dosage of 1 gm. per day. This was reduced to 0.75 gm. per day after the first month, since the patient claimed that the fourth 250 mg. capsule made her irritable and caused a slight elevation in temperature. Between July 1958 and April 1959 the patient took, on the average, only about 0.25 gm. of penicillamine daily, as judged from the amount of drug she used. Nevertheless, rapid marked improvement in her tremors was noted. By September 1958 only a mild resting tremor of the outstretched fingers of the left hand was present. (Fig. 2.) Finger-to-nose test showed terminal tremor bilaterally and there was no rigidity. In addition to her household duties she considered taking a part-time job. Except for one episode of probable splenic infarction in April 1958, there have been no significant abdominal complaints. The Kayser-Fleischer rings have remained prominent on slit-lamp examination.

Her infant is apparently perfectly normal as was true of two other patients with Wilson's disease who had babies [*78,79*]. His serum ceruloplasmin was 34 mg. per 100 ml. at the age of nine months.

CASE V. J. B. was found to have hepatosplenomegaly of unknown etiology at the age of nine years. At sixteen she noted tremors of her head and of her left hand. These became worse with emotional "pressures." She was extremely insolent to her parents and had violent outbursts of ungovernable temper.

Her earlier history revealed no abnormalities, and included a tonsillectomy at three, measles and mumps. Because of her severe emotional maladjustment she entered into treatment with a psychoanalyst when she was fifteen years of age and, with interruptions, such treatment has continued to the present. Testing and interviewing by a clinical psychologist confirmed the impression that she is schizophrenic.

The patient is the daughter of healthy, unrelated Jewish parents. The father was forty-eight and the mother forty-one in 1956. A sister, six years younger than the patient, has no history of hepatic or neurologic disease, and is the only sibling.

When first seen in 1956, at the age of seventeen, the patient appeared to be a tanned, healthy-looking, well developed girl who walked with a slightly stiff, jerky movement. Her upper lip was slightly retracted, but there was no drooling. There was a coarse, uncontrollable tremor of both outstretched hands, worse on the left. Finger-to-nose test showed some decomposition and terminal tremor. Considerable adiadochokinesia was present. There was a fine nodding tremor of her head. Her speech was explosive with a peculiar staccato quality. Brown, thick and opaque Kayser-Fleischer rings were noted bilaterally. Both the margin of the liver and the splenic tip were felt with difficulty. Laboratory studies showed absence of detectable serum ceruloplasmin and a serum copper of 46 μg. per cent. Other results are given in Table I. Gastrointestinal series showed a considerably enlarged spleen and probable varices of the lower esophagus.

Penicillamine therapy was begun in December

1956. Within a week her temperature rose to 102°F., she became sleepy, and a maculopapular eruption appeared on the backs of her fingers, her cheeks and most of her trunk. Her hemoglobin, white blood cell, differential and platelet counts were within normal limits. The reaction subsided and, at first with the administration of prednisone and later without it, she was able to take penicillamine regularly. The only reaction which appeared subsequently and recurred several times was thrombocytopenia (to as low as 4,000 per cu. mm.) and bruising, neither of which ever persisted when penicillamine was discontinued. By September 1957 she was much improved. The tremors of the hands and the head could no longer be detected. Her handwriting had improved markedly, her speech was essentially normal, and finger-to-nose testing, rapid alternating movements, and tying of shoelaces were all carried out smoothly and with no perceptible difficulty. No hematomas were visible although platelets were only 26,000 per cu. mm. There was, however, no change in the hepatosplenomegaly nor in the Kayser-Fleischer rings at that time. A slight decrease in the intensity of the latter was noted in September 1958. The neurological improvement has persisted up to the present (April 1959) and penicillamine administration, without resin, is being continued more or less regularly, depending on the patient's whims.

CASE VI. W. G. was ten months old when first seen in October 1954. He was entirely asymptomatic but was investigated because he was a sibling of a patient (Case II). Physical examination did not disclose any abnormalities. Laboratory examination showed absence of plasma ceruloplasmin. Other results are given in Table I. Urinary amino acids were within normal limits qualitatively and quantitatively.

At the age of one year the patient was given a low copper diet and one teaspoonful of Carbo-Resin with each meal. In December 1956, when he was a little over two years old, the patient was given 0.4 gm. of penicillamine daily, which was increased to 0.5 gm. daily in May 1957, 0.7 gm. daily in June 1957, and 1 gm. daily in June 1958.

In October 1957 an open biopsy of his liver was performed at Babies' Hospital of the Columbia-Presbyterian Medical Center [*58*]. The liver was grossly normal and showed no definite histologic abnormalities except, perhaps, for the presence of many glycogen nuclei. However, the copper content of the liver was 271 μg. per gm. of wet weight, which is to be compared with a normal value of about 7 μg. per gm. of wet weight [*10,67–70*]. A second liver biopsy was performed in November 1958 at Babies' Hospital. Again the liver seemed grossly normal with a "slightly irregular . . . yellow-tan" color. Microscopically glycogen nuclei was seen in moderate numbers and slight fibrosis was observed in "the portal areas and the walls of the sinusoids." The overall impression was that of a "liver with minimal fibrosis." The copper content had not decreased significantly in the year of penicillamine therapy. It was 244 μg. per gram of wet weight.

To date he has shown no clinical or chemical signs of neurologic or hepatic disease.

COMMENTS

We shall discuss these observations and results by summarizing the manifestations of Wilson's disease in our patients, describing treatment and its pharmacologic effects, and evaluating the clinical results of treatment.

Manifestations of Wilson's Disease in the Patients. Five of our six patients exhibited most of the signs and symptoms which have been described as part of hepatolenticular degeneration [*1*]. The sixth patient (W. G.), requires discussion apart from the others since he has none of the symptoms of the disease.

Except for this patient (W. G.) all our patients have a similarity in appearance due primarily to the tendency of the upper lip to be retracted and the upper teeth to be exposed. This appearance occurs so early in the disease and is so characteristic that it is possible to diagnose a patient tentatively by this observation when he is first seen.

Neurologic symptoms and signs were present in these five patients and were the cause of most of their suffering. Tremors, rigidity or incoordination of the arms, hands, tongue, mouth and legs and drooling were present in varying degrees. The three adolescent patients (G. G., D. W. and J. B.) had severe emotional and behavioral difficulties. It was our impression, as well as that of two clinical psychologists who interviewed them, that these were only partly explicable as the reactions of adolescents to a crippling and life-threatening disease. It seems possible that this psychiatric symptomatology is, in part at least, also the result of damage to the central nervous system by the underlying disorder.

Four patients had enlargement of the liver and spleen at some time during their course. Splenomegaly with evidence of a shrunken liver occurred in one patient (D. S.). Esophageal varices were observed in three patients (D. S., G. G. and J. B.). An episode of hematemesis which may have been related to these occurred in one patient (D. S.). Spider angiomas were found in two patients (D. S. and R. P.), and jaundice and ascites appeared in one patient (R. P.) dur-

TABLE II
CUPRIURIC EFFECT OF PENICILLAMINE IN FIVE PATIENTS WITH WILSON'S DISEASE

Patient	Duration of Treatment (days)	Total Penicillamine Taken (gm.)	Estimate of Excess Copper Excreted with Penicillamine Therapy (mg.)
D. S.	546	894	410
G. G.	516	665	459
D. W.	660	2,028	950
R. P.	493	190	464
J. B.	685	909	474

ing and after a pregnancy at the end of which she delivered a healthy boy. Two patients (D. S. and D. W.) suffered from recurrent attacks of abdominal pain which, although of unknown cause, may have reflected hepatic disease. Various liver function tests indicated that four patients (D. S., G. G., D. W. and R. P.) had a moderate degree of hepatic dysfunction [*59*]. (Table II.)

Three patients (D. S., D. W. and J. B.) suffered from hypersplenism at some time during their course, as evidenced by thrombocytopenia, leukopenia and mild anemia.

There were several miscellaneous signs and symptoms in these patients most of which have previously been reported in Wilson's disease. All of them had Kayser-Fleischer rings when they were first seen. We believe that these greenish or brownish rings, or crescents, which are probably deposits of copper in Descemet's membrane, are present in all untreated patients in whom other manifestations of Wilson's disease have developed. If their absence in such a patient is demonstrated by slit-lamp examination, we hesitate to make the diagnosis. Evidence of renal disease, which was not however clinically significant, was seen in the increased excretion of amino acids in the urine of five patients [*7,41,60–62*]. (Table I.) Other renal manifestations such as phosphaturia, uricosuria [*62–64*], glycosuria [*30,62*] and diminished glomerular filtration [*62,65*], as well as the osseous changes [*20,21,83*] which may be due to renal dysfunction, have been described as being characteristic of some patients with Wilson's disease but these were not looked for systematically in our patients.

Hemolytic anemia, which has been described in patients with Wilson's disease [*10*], may have been the earliest manifestation of the disease in one patient (R. P.). Recurrent and troublesome headaches were complained of by two patients (D. S. and D. W.) but their relation to the disease is unclear. One patient (D. S.) has always been noted to have multiple premature ventricular beats. None of these patients exhibited the azure lunulas which Bearn and McKusick [*19*] have described.

One patient (W. G.) has been included in the case reports because we believe he has asymptomatic Wilson's disease and represents the type of subject in whom treatment has the greatest potential value. Presumably the deposition of excessive copper begins in infancy, if not *in utero*, in those subjects in whom Wilson's disease is destined to develop, and irreversible tissue damage should be most effectively avoided by minimizing this deposition as early as possible. Therefore, this patient has been treated from the age of ten months, when his aceruloplasminemia was first discovered, as though he had Wilson's disease despite the absence of any symptoms or clinical signs. How may the diagnosis of the disease be made in such a person. The reasonable certainty that Wilson's disease will develop, at least if he is untreated, rests on the following facts: (1) the patient like his ill sister (G. G.), has completely lacked plasma ceruloplasmin every time an analysis has been made, whereas above the age of six months normal infants have concentrations of plasma ceruloplasmin greater than about 20 mg. per 100 ml. [*66*]; (2) two healthy sisters, fifteen and twenty-three years of age, and both parents have normal concentrations of plasma ceruloplasmin; (3) analysis of biopsy specimens of his liver obtained when he was three and four years of age showed that it contained, respectively, 271 and 244 μg. of copper per gram of wet liver in comparison to a normal concentration of about 7 μg. per gram [*10,58,67–70*]; and (4) the patient (G. G.) showed no symptoms of Wilson's disease until she was twelve years old. Therefore, if the pathogenesis of Wilson's disease outlined in this paper is correct, and if the regimen described effectively prevents excessive copper absorption and promotes copper excretion, the illness should not develop; at the least, the development of manifest disease should be delayed until considerably later than the age of twelve years.

Many of the manifestations of the disease in

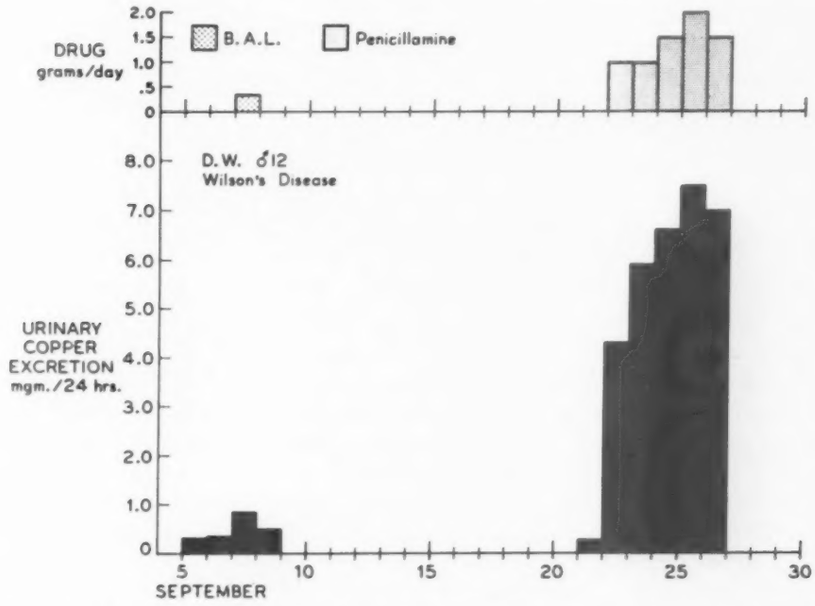


FIG. 3. Cupriuric effect of BAL and penicillamine therapy in a patient (D. W.) with Wilson's disease. The 0.3 gm. of BAL was administered intramuscularly as 3 cc. of a 10 per cent solution in peanut oil. The penicillamine was given orally.

these patients which can be detected by biochemical or clinical pathological tests are indicated in Table I.

Treatment. As already indicated, specific therapy was directed toward: (1) diminishing the absorption of dietary copper, and (2) promoting the excretion of copper from the body.

We attempted to minimize copper absorption by prescribing a diet which contained as little copper as practicable* and by adding to meals a carboxylic cation exchange resin to bind, and excrete through the feces, whatever copper was in the food.

To promote copper excretion [*38*] we initially administered intramuscular injections of BAL. When Walshe's studies [*52*] indicated that penicillamine, given orally, could cause the urinary excretion of considerably more copper than could a practicable daily dose of BAL (Fig. 3) we substituted continual therapy with penicillamine for BAL. We could see no practical or theoretical advantage in interrupting therapy, except for toxic reactions or unavailability of the drug, since any gain in increased copper excretion after a period without treatment seemed likely to be offset by the diminished excretion of copper during the interruption.

Despite our intention to administer therapy continually, it proved to be virtually impossible to do so. BAL could not be given daily because of pain and toxicity manifested by nausea, vomiting, dizziness and headaches [*6,12,41*] (D. S., G. G., D. W. and R. P.). Resin therapy was refused intermittently by all six patients, most persistently by three patients (D. S., D. W. and J. B.), because it was too unpalatable or caused nausea. Penicillamine therapy resulted in a generalized reaction with fever, rash and adenopathy in two patients (G. G. and J. B.) when it was first administered. Further, in both of these girls and in another patient (D. W.), penicillamine caused alarming thrombocytopenia and leukopenia on occasions [*71*]. Fortunately, these reactions improved promptly when penicillamine administration was temporarily discontinued. Therapy was also interrupted in one patient (G. G.) when a severe iron-deficiency anemia developed which seemed to have resulted from menstrual blood loss plus the iron-depleting effects of the diet, and the administration of resin and BAL [*38*]. Although it never required cessation of penicillamine administration, in three patients (G. G., D. S.,

* Foods to be avoided because of high copper content [*53*] include: liver, chocolate, cocoa, nuts, mushrooms, molasses, dried peas, broccoli, shellfish, Dextri-Maltose, certain cereals (Bemax, All-Bran, Mead's Cereal and Pablum, refined wheat breakfast cereal). The regional drinking water should be analyzed. If it contains 1 p.p.m. of copper (1 μg./ml.) or more, it is probably advisable for the patient to drink distilled or demineralized water.

D. W. and J. B.) a non-erythematous desquamation, chiefly on unexposed skin and face, developed while penicillamine was given regularly. It is a tribute to the spirit of these patients that, despite these difficulties and the necessity for frequent blood counts, treatment was carried out as faithfully as it was.

Although we shall mention subsequently other therapeutic agents which we used briefly, the basic regimen that these patients were given has just been described. Its pharmacologic effectiveness was difficult to assess largely because copper balance studies, which are tedious and unreliable [*10*], were not made. Consequently, we did not know the amount of dietary copper ingested or the portion of it which was excreted in the feces. Thus we could not be certain of the value of the diet and the resin which were prescribed.

On the other hand, the effect of penicillamine, or BAL therapy, on copper excretion can be precisely determined since both act by increasing the urinary output of copper. At intervals a twenty-four hour urine collection was made in copper-free glassware by each patient except one (W. G.) in whom only partial collections were possible. An aliquot was analyzed for copper, permitting calculation for the total excretion of that day. These results are given in Figure 4 for five patients; for one patient (W. G.) urinary copper concentrations are indicated.

It is apparent that the effectiveness of penicillamine therapy diminished markedly with time in all subjects. For example, when 1 gm. of penicillamine was first administered to one subject (D. W.) he excreted 5.9 mg. of copper in twenty-four hours. After being given almost continual penicillamine therapy for six months the administration of 4 gm. of penicillamine resulted in excretion of less than 1 mg. of copper in twenty-four hours. Similar findings were noted in all the other patients. (Fig. 4.)

The reasons for this tachyphylaxis, which has also been noted with the administration of BAL [*10,50*], are not clear but we believe that the greater magnitude of the initial cupriuria is due to a relatively small amount of copper which is loosely bound in comparison to the bulk of the tissue deposits of copper. Certainly the copper which was excreted in the first months of treatment in our patients did not reduce tissue copper concentration to normal levels, as is clear from the analyses of liver copper in one subject (W. G.). Further, it does not appear that destruction of penicillamine, in plasma at least, is increased by regular administration of the drug. The estimation of penicillamine in plasma, by titration of free sulfhydryl groups, following a single dose (1 gm.) in a patient who had been given the drug regularly for a year, and in a control subject who had never received it previously, indicated that the plasma concentration of penicillamine was approximately the same in both subjects.

Despite the lack of balance studies we have attempted to calculate roughly how much copper was removed from these patients as a result of penicillamine therapy. To do this we have assumed that administration of penicillamine resulted in the urinary excretion of a_1 mg. of copper in a period of t_1 days. In the same number of days we assume that b_1 mg. would have been excreted had no penicillamine been given. The value of a_1 for a period during which a constant daily dose of penicillamine was taken is calculated by multiplying the average of the twenty-four–hour urinary copper excretions, measured at the beginning and end of the period, by t_1. The value of b_1, for the same period, is calculated by multiplying the twenty-four–hour urinary copper excretion, measured on a day in or close to this period, when no penicillamine was taken, by t_1. The difference between a_1 and b_1 is called c_1 and represents the excess copper which can be considered to have been excreted with penicillamine. The sum of $c_1, c_2, c_3 \ldots c_n$ for all the periods during which the patient was given penicillamine, $t_1, t_2, t_3, \ldots t_n$ equals $\sum_{i=1}^{i=n} c_i$ and is taken as a measure of the total excess excretion of copper by penicillamine. The results of these calculations for our five symptomatic patients are given in Table II.

It is clear that these results can serve as nothing more than rough approximations, since unrecorded variations in the amount of penicillamine given or in its absorption, changes in diet, irregularities of response from day to day and variable fecal excretion of copper could produce changes in copper balance which we cannot take into account. Nevertheless, the results indicate that therapy resulted in the excretion of considerable amounts of copper relative to the quantity deposited in tissues. For example, the livers of patients with Wilson's disease may contain about 150 mg. or more [*72*]

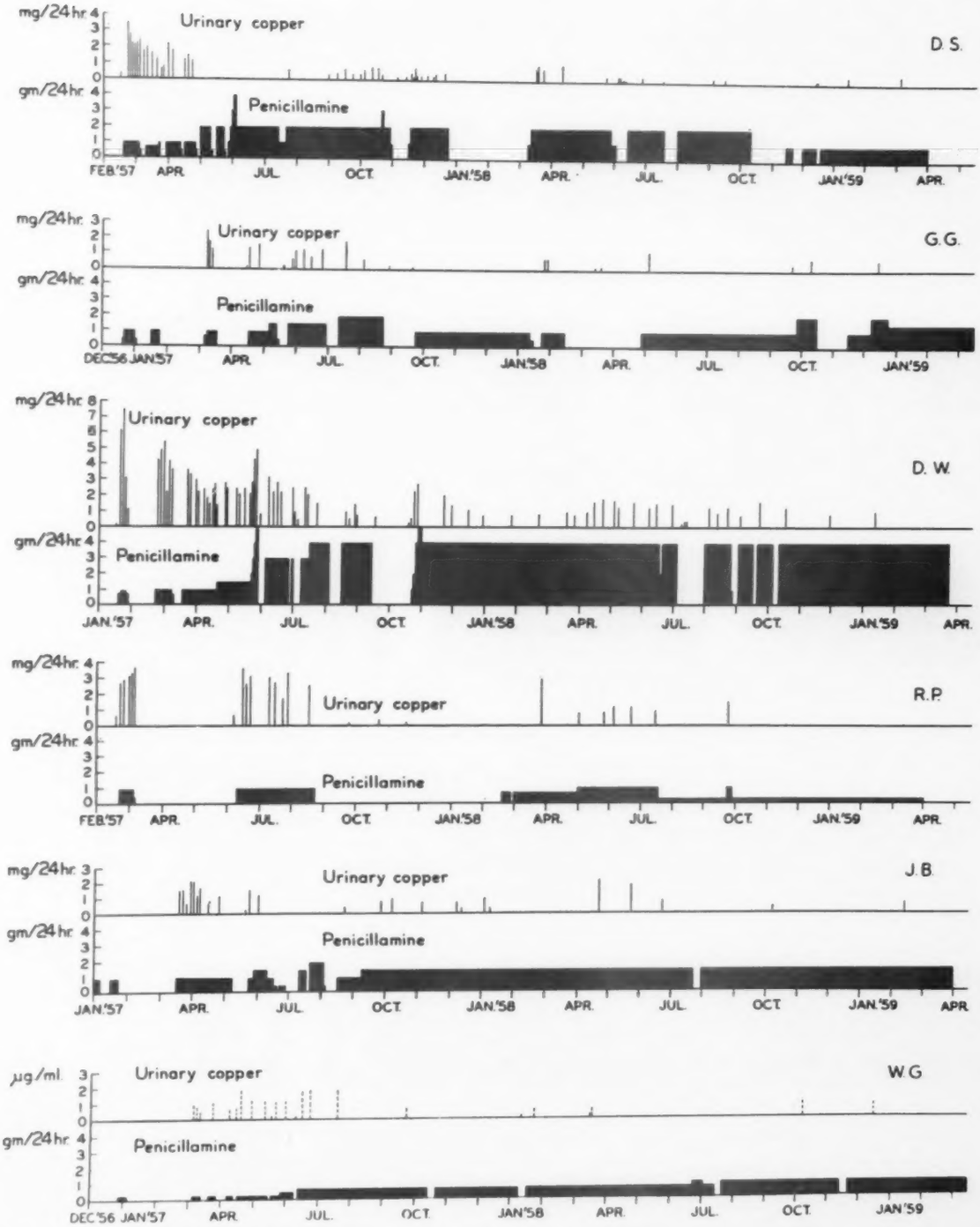


FIG. 4. Urinary copper excretion in relation to administration of penicillamine in six patients with Wilson's disease. Excretion is given as milligrams of copper per twenty-four hours except in Case VI (W. G.) in which urinary copper concentrations are indicated.

and there may be an equal amount in the rest of the body.

It is also apparent from these calculations that penicillamine therapy is far from ideal in its capacity to promote the excretion of copper. *In vitro* experiments indicate that one molecule of copper combines with two molecules of penicillamine so that 1 gm. of penicillamine (molecular weight, 149) should theoretically be followed by the excretion of about 210 mg. of copper (atomic weight, 63). In practice, as is apparent from Figure 4, the amount of copper excreted following this dose of penicillamine is closer to 2 mg. Furthermore, we have shown in one patient that intravenous administration of the drug results in no greater excretion of copper than oral administration of the same dose; Walshe has demonstrated the same [*52*].

Other therapeutic agents: For theoretical or empirical reasons we have, on various occasions, tested the therapeutic effectiveness of four other agents in preventing copper absorption or promoting its excretion.

(1) Since other proteins which are deficient on an hereditary basis, such as antihemophilic globulin, gamma globulin and fibrinogen, can be replaced with good therapeutic effect [*73*], we investigated the chemical and clinical results of raising the serum ceruloplasmin concentration to normal in two patients (D. S. and G. G.)* [*74*]. The results of these trials, in two sets of studies utilizing radioactive copper^{64}, indicated that the patients so treated absorbed copper essentially in the same manner and to the same extent ceruloplasmin was absent or in normal serum concentration. Their clinical symptoms and signs also were unchanged despite the normal amounts of serum ceruloplasmin. Similar clinical results have already been reported by Bickel and his co-workers [*75*].

(2) Because ascorbic acid reacts readily with cupric ion, by which its oxidation is catalyzed, we wondered whether or not ascorbic acid would modify the cupriuric effect of penicillamine. One hundred milligrams of ascorbic acid was given to one subject (D. S.) three times during one day when 2 gm. of penicillamine was administered. She excreted 0.22 mg. of copper that day. On the two days before and after this trial the same dose of penicillamine resulted in the excretion of 0.44 and 0.22 mg., respectively, indicating that ascorbic acid had no effect on copper excretion.

(3) Penicillamine,† which is quite expensive, can be made more cheaply either as its acetone adduct or as N-acetyl penicillamine. The acetone adduct† was given to one patient (D. W.) and the N-acetyl penicillamine† to another patient (D. S.). Neither produced any significant increase in urinary copper excretion.

(4) A recent report [*76*] indicated that 1 mg. of vitamin B_{12} increased the daily excretion of urinary copper to 7 mg. in a patient believed to have atypical Wilson's disease. We repeated the experiment, even though the authors' interpretation of their results that B_{12} acted by binding and excreting copper in place of cobalt is, for stoichiometric reasons, obviously incorrect. One milligram of B_{12} was given intramuscularly on each of three days and this resulted in the excretion of 0.13, 0.22 and 0.09 mg. of copper, values essentially the same as those found without therapy.

Two agents which other investigators have used are potassium sulfide [*9,10,40*] and calcium disodium ethylenediaminetetraacetate (Versene) [*7,8,10,12,30,37,46*]. The former is capable of precipitating dietary copper in the gut as the insoluble sulfide, with resultant fecal excretion. The ease of administration of this compound in capsules containing 20 mg. makes it much more attractive than Carbo-resin. Versene increases urinary copper excretion in a manner similar, presumably, to BAL and penicillamine. Unfortunately, it seems to be significantly effective only when given intravenously [*10–12*].

Clinical Evaluation of Treatment. Evaluation of therapy of this disease is complicated by the facts that the illness appears insidiously over the course of ten, twenty or more years and, if untreated, is characterized by spontaneous remissions and exacerbations in its course. Thus in 1954, before it was even known that the patient (G. G.) had Wilson's disease, she became almost completely paralyzed and then largely

* Ceruloplasmin, Lot No. CH-131, was prepared in purified, sterile, non-toxic and non-pyrogenic form under the direction of Dr. H. O. Singher of Ortho Research Foundation, Raritan, New Jersey. Fraction IV of human plasma was the source of the ceruloplasmin and was obtained through the kindness of Dr. Sam T. Gibson, Director, American National Red Cross Blood Program, and Dr. James A. McComb, Director, Dr. John M. Newell and Mr. Lewis H. Larsen of the Massachusetts Public Health Biologic Laboratories.

† The penicillamine and its derivatives which we have used were synthesized under the direction of Dr. Alfred Bader of the Aldrich Chemical Company, Milwaukee, Wisconsin.

recovered from the paralysis with no therapy. Another subject (D. W.), on the other hand, showed unmistakable progression of his neurologic symptomatology in the nine months from August 1956 to May 1957 despite intensive therapy which included BAL and penicillamine. Nevertheless, we believe that certain clinical developments can be related to treatment with BAL or penicillamine. Diet and resin therapy, on the other hand, do not seem to produce observable clinical changes over a short enough time to separate them from the vicissitudes of the natural history of Wilson's disease.

The administration of BAL or penicillamine resulted in observable clinical changes of two kinds. The first was an exacerbation of neurological symptoms and signs in several patients during therapy; the second was improvement in these manifestations occurring either during treatment or following its interruption. Three patients (D. S., G. G. and R. P.) showed a distinct increase in their neurological symptoms and signs during most of the courses of the administration of BAL. A similar effect was noted with the administration of penicillamine in one patient (R. P.).

During the entire period of treatment and observation four patients (D. S., G. G., R. P. and J. B.) have shown marked neurologic improvement in all of their manifestations. (Figs. 1 and 2.) One subject (D. S.) is ready to begin working again; four years ago her neurologic symptoms and signs resulted in loss of her job. The second subject (G. G.) is regularly attending high school; three years ago it appeared as though she would have to withdraw permanently. The third subject (R. P.) has been married, had a baby and manages to take care of her house and family unaided; three years ago her tremors and incoordination rendered her almost useless in the home. In the fourth subject (J. B.) her tremor, chiefly of the head, has virtually disappeared except when she becomes excited or anxious. She is attending school and working only intermittently but her chief disability is the result of her psychiatric condition. This has improved somewhat, too, although it is impossible to determine how much of this has been due to the psychiatric treatment she has been receiving. It is also difficult to assess the effects of therapy on the emotional aspects of the disease in two subjects (G. G. and D. W.), although they have both shown definite improvement.

The next most striking result of therapy has been the changes noted in the Kayser-Fleischer rings. In two subjects (D. S. and G. G.) prominent rings have practically disappeared, even to slit-lamp examination. In two other subjects (D. W. and J. B.) there has been a moderate decrease in their intensity; in one subject (R. P.) no definite change has been noted. It is worth pointing out, in view of the evidence that these rings represent tissue copper deposits [*18*], that their complete or partial disappearance strongly suggests that the copper content of at least some tissues has been reduced by therapy [*6*].

There have been no observable beneficial effects of therapy on the liver and spleen of our patients. Neither spider angiomas, splenomegaly, hypersplenism nor the generally moderate laboratory evidence of hepatic dysfunction have perceptibly improved and, in fact, one subject (D. W.) has shown unmistakable progressive splenomegaly. The only suggestion that therapy may have improved the hepatic pathology at all may lie in the fact that there has seemed to be a decrease in the frequency and severity of attacks of abdominal pain in two subjects (D. S. and D. W.). However, we have never been certain that these attacks are due to hepatic disease.

Little effect of therapy has been observed in the biochemical and clinical pathological tests shown in Table 1.

The improvement noted in these patients has not seemed to parallel the cupriuria which therapy has induced. We cannot say, for example, that penicillamine produced greater amelioration of signs and symptoms when first administered than later, despite the much greater effect on copper excretion noted at first. (Fig. 4.) Other authors [*12,30,71*] have commented on this lack of correlation of copper excretion and clinical improvement.

In the past decade there have been a number of other clinical studies in which the effects of removing copper from patients with Wilson's disease have been studied. Most of these have been investigations in which cation-exchange resins [*8,11*], potassium sulfide [*9,10,40*], copper-poor and protein-rich diets [*41*], BAL [*5–13,22–37,39–49*], Versene [*7,8,10–12,30,37,46*], and a number of more empirical agents have been used [*12,35,76*]. Of these agents BAL has probably had the widest use. The conclusions of different authors are in disagreement as to the

therapeutic efficacy of regimens based on BAL, with or without other agents, probably partly because of the difficulty in obtaining even several patients for prolonged study and partly because of the same factors which we have mentioned as complicating evaluation of treatment. In 1951 Denny-Brown [*6*] published the results of a study of prolonged BAL therapy in five patients. Treatment produced a remarkable degree of reversibility in the neurological symptoms and Kayser-Fleischer rings. Other authors have [*10,12,41*] been rather less impressed with the long term effects of BAL and have commented on the difficulties attendant upon its administration.

The administration of penicillamine has been evaluated clinically for an appreciable period of time only in the studies of Seven, Kliman and Peterson [*56*], and Fister, Boulding and Baker [*54*]. Of two patients treated by the former group for ten months with 2 gm. of penicillamine daily "one . . . showed continued progression of his disease during therapy. The other showed a dramatic clinical improvement." The patient treated by Fister, Boulding and Baker had become worse under treatment with BAL, Versene, high protein diet and potassium sulfide. Penicillamine therapy was instituted at a time when he was "almost moribund," and "the response was dramatic." Improvement continued for the nine months of therapy which the report covers despite evidence of some tachyphylaxis with respect to cupriuria. We believe that the other instances [*52,57*] in which penicillamine therapy has been used for Wilson's disease have been of too brief a duration to permit evaluation of the clinical results.

It would be misleading if we did not add that in three of our patients we have the impression of a general deterioration, over the years, which is difficult to define precisely. One patient (D. S.) has lost weight, her cheeks have taken on a sunken appearance, she has become increasingly stoop-shouldered and it is clear when she is compared, by means of motion pictures, to her condition four years ago that she is not doing as well as she was then. The net effect of the development of neurologic signs in the second patient (D. W.), followed by improvement while receiving therapy, has been to leave him obviously sicker than he was when first seen. The third patient (R. P.) has gained body weight but her face, too, has a somewhat hollower and less healthy appearance than it once had. Two patients (G. G. and J. B.), on the other hand, have seemed to escape such insidious effects of the disease and, possibly, of its treatment.

One patient, who is not included in this report, died at the age of sixteen about two years after a spleno-renal shunt and splenectomy were performed for hemorrhaging varices. He was never given intensive therapy, however, because he refused to accept regular BAL injections, and penicillamine was available only in small quantities until shortly before his death. Clearly, final evaluation of the efficacy of the regimen outlined in this paper will depend in large measure on how long the patients being treated survive, since Wilson's disease has always been progressive and fatal.

In one group of subjects, of whom the patient (W. G.) is an example, the prevention of excessive net copper absorption and the removal of copper should be of the greatest value. These are the infants or children who have a marked persistent deficiency or absence of ceruloplasmin without known cause [*84–86*], and who have not yet shown any symptoms or other signs of Wilson's disease. These children can be easily and rapidly detected by means of a spot test, and perhaps all infants ought to be subjected, at least once, to such a screening test for ceruloplasmin deficiency [*77*]. Confirmation of the finding of a marked persistent deficiency of ceruloplasmin almost makes certain the eventual development of Wilson's disease. Modifying the child's environment to make it, and him, freer of copper may make it possible to avoid the fatal disease to which his heredity predisposes him.

SUMMARY AND CONCLUSIONS

1. Based on the postulate that Wilson's disease is the result of the deposition of toxic amounts of copper in various tissues, six patients have been treated from three to five years with a regimen designed to minimize absorption of dietary copper and to promote the excretion of copper already deposited in the body.

2. Although the effects of this regimen are difficult to evaluate, it is believed that there has been definite clinical improvement in four of these patients, and probable improvement in the fifth. The sixth patient is a child of five years who has not yet shown symptoms of the disease but in whom if untreated, Wilson's disease would probably develop.

3. Improvement of neurological symptoms and signs, and disappearance or fading of

TABLE III
REGIMEN FOR THE TREATMENT OF WILSON'S DISEASE

To minimize copper absorption
A copper-poor diet
Potassium sulfide, 20 mg., with each meal
To promote urinary copper excretion
Penicillamine, 1 to 4 gm. daily, in divided doses, on an empty stomach

Kayser-Fleischer rings have been the most noteworthy effects of treatment. Hepatic function has shown no improvement in any of our patients.

4. Our findings suggest that until a more effective regimen is found, the one herein outlined (Table III), or one similar to it, should be used vigorously and continually in patients with Wilson's disease, as well as in those asymptomatic aceruloplasminemic children in whom the disease is probably destined to develop.

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Central Nervous System Syndromes of "Viral" Etiology*

A Study of 713 Cases

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THIRTY years ago the etiologies of infectious encephalitis and aseptic meningitis were unknown, and it was generally assumed that each syndrome represented a discrete etiologic entity differentiated only from uniformly fatal rabies and paralytic disease caused by polioviruses. In 1933, however, St. Louis encephalitis virus was isolated from the brain of seven patients dying of epidemic encephalitis [*1*] and in 1935 the lymphocytic choriomeningitis (LCM) virus [*2*] was recovered from the cerebrospinal fluid of two patients with benign aseptic meningitis [*3*]. During the years since these original observations, multiple viruses as well as certain bacteria and fungi have been implicated in the genesis of each syndrome; indeed, over fifty immunologically distinct agents have been associated with aseptic meningitis and encephalitis occurring both sporadically and in epidemics. Thus, while the clinical entities are known to be of multiple etiology, the relative importance of each of these varied agents in the year-round occurrence of acute infections of the central nervous system has remained obscure.

It is the purpose of this report to provide the clinician with perspective into the etiology of aseptic meningitis, encephalitis and paralytic disease by summarizing the experience of this laboratory with these syndromes. The relative frequency with which specific viruses, bacteria and fungi are related to each syndrome, and the annual and seasonal variation in their association with infections of the central nervous system, are described.

METHODS

Patients. The 713 patients in this study were admitted to military and Veterans Administration hospitals with acute infections of the central nervous system of presumed viral etiology between January 1953 and January 1958. Approximately 80 per cent of these patients were hospitalized in the continental United States; the remaining 20 per cent were hospitalized in Hawaii, Europe, the Far East and Puerto Rico. Racial origin and socioeconomic status of patients corresponded to those of the U. S. population at large; patients ranged from newborns to the aged, but the majority were children and young adults; sex distribution was unequal, with a male to female ratio of 1.5:1. Disease in approximately 90 per cent of patients occurred sporadically; the remainder occurred during epidemics of CNS disease.

Criteria for Inclusion in Study. Patients were included in the study if they fulfilled the following criteria: (1) Sufficient clinical information was provided to the laboratory to ascertain that the patient had suffered an acute infectious disease with CNS manifestations of apparent viral etiology. (2) Specimens adequate to attempt definitive etiologic diagnosis were provided. These included at least 3 ml. each of serum samples, one usually obtained before the seventh day of disease (acute phase) and one or more serum samples obtained after the fourteenth day of disease (convalescent phase). In patients who

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TABLE 1

PROCEDURES FOR DIAGNOSIS OF "VIRAL" DISEASE OF THE CENTRAL NERVOUS SYSTEM (WALTER REED ARMY INSTITUTE OF RESEARCH 1953 TO 1958)

Agent	For Immunologic Diagnosis							For Recovery of Agent					
						Cell Culture		Animals			Embryonated Eggs		Cell Culture
	Complement Fixation	Hemagglutination Inhibition	Microagglutination Lysis	Mouse Neutralization	Chorioallantoic Membrane Neutralization	Metabolic Inhibition Neutralization	Tube Neutralization	Suckling Mice	Adult Mice	Guinea Pigs*	Amniotic and Allantoic Sac	Chorioallantoic Membrane	Monkey Kidney and KB [8] or HeLa [9]
Mumps	++	+					+				++		++
LCM	++			++					++	++			
Herpes simplex	++				+		+	++	++			++	++
Arthropod-borne viruses	++	+		++				++	++				
Poliomyelitis						++	+						++
Group A Coxsackie	+							++					
Group B Coxsackie						++	+	+					++
ECHO						+	++						++
Leptospirosis†	+		++					(Not attempted from human specimens)					

NOTE: ++ = Procedures of choice—always performed when appropriate specimens available.
+ = Supplementary procedure employed in selected instances.

* Guinea pigs inoculated with cerebrospinal fluid or central nervous system tissue observed for six weeks, autopsied and examined for M. tuberculosis.

† Performed by Division of Veterinary Medicine, Walter Reed Army Institute of Research.

died, submission of necropsy specimens alone was considered adequate for inclusion.

During this study the frequent association of enterovirus infections with CNS disease became apparent, and since their diagnosis depends primarily on isolation of virus from the patient, submission of stool, throat washings and cerebrospinal fluid was encouraged.

Each case history was reviewed by a physician prior to study, in order to plan the sequence of diagnostic tests. This plan, utilizing the technics to be described, was individual for each patient and was guided by clinical findings, the season of the year and current epidemiological information. After the laboratory study was complete, the hospital chart or detailed summary of hospital course was requested for review to determine the subsequent clinical course and outcome.

Specimens. All specimens for virus isolation were frozen as soon after collection as possible and shipped and stored in dry ice (−70°C.) until tested. Serums were separated from the clot aseptically at the referring hospital and shipped to this laboratory via air mail at room temperature; they were stored at −20°C. upon receipt.

Diagnostic Tests. The serologic and virus isolation technics employed for diagnosis are described in detail elsewhere [4–7] but are summarized in Table 1.* The complement fixation test was used for diagnosis of mumps [5,10] and herpes simplex virus [11] infec-

* All cell cultures and culture media were obtained from Microbiological Associates, Bethesda, Maryland. Rabbit neutralizing antiserums for the Coxsackie virus serotypes B-1 to B-5 inclusive were obtained from the same source. Complement-fixing antigens for mumps, lymphocytic choriomeningitis, Eastern equine encephalitis, Western equine encephalitis, St. Louis encephalitis and Japanese encephalitis were prepared by both Lederle Laboratories, Pearl River, New York, and this laboratory. Adenovirus complement-fixing antigen was purchased from Parke, Davis and Company, Detroit, Michigan, and Microbiological Associates. The psittacosis-lymphogranuloma venereum group complement-fixing antigen was prepared by E. R. Squibb & Sons, New York. All other antigens and antiserums were prepared by WRAIR. All reagents were carefully standardized before use.

tions. Neutralization tests in cell cultures constituted the serologic method of choice for poliomyelitis [*12,13*], Group B Coxsackie [*13*] and ECHO (enteric cytopathogenic human orphan) viruses [*5*]. For LCM and the arthropod-borne virus infections, both the complement fixation and virus neutralization tests [*7*] were routinely employed. The microscopic agglutination-lysis technic [*14*] employing eighteen test strains was used for the diagnosis of leptospirosis.

When indicated (for example in patients from endemic areas) further serologic tests for evidence of infection with Histoplasma capsulatum, Blastomyces dermatitidis and Coccidioides immitis were performed using both complement fixation and collodion agglutination technics [*15*].* Complement fixation tests for adenovirus infection [*16*], toxoplasmosis [*17*], the psittacosis-lymphogranuloma venereum group [*18*], various rickettsial diseases [*6,19*] and neutralization tests for encephalomyocarditis virus infection [*20*] were similarly employed with serums of certain undiagnosed cases. Heterophil† [*21*], Streptococcus MG and cold agglutinin titers [*6*] were determined for patients when indicated on clinical grounds.

Interpretation of Test Results. A patient's infection was considered to be associated with a specific agent if (1) a fourfold or greater increase in complement fixation, hemagglutination inhibiting, neutralizing or agglutination-lysis antibody occurred during the course of illness; (2) a tenfold increase in neutralization index, to final indices of 100 or more, could be demonstrated between acute illness and convalescence; or (3) an infectious agent could be recovered from tissue obtained at autopsy and the pathological findings were consistent with the laboratory diagnosis.

These basic criteria for interpretation had but two major exceptions. In mumps "meningoencephalitis" with parotitis, a complement fixation antibody titer of 1:64/0.25 ml. or greater was interpreted as indicative of recent infection. The presence of antibody to poliovirus, without significant increase, was also interpreted as indicative of recent infection in patients with lower motor neuron paralysis from whom poliovirus was recovered. Minor exceptions to these criteria in twenty-four individual patients are enumerated in the footnote of Table VIII. Isolation of an infectious agent from cerebrospinal fluid without supporting serologic evidence of infection was considered conclusive evidence of infection only in tuberculous meningitis.

All serum specimens from patients without etiologic diagnosis were tested (insofar as serum quantities permitted) for evidence of infection with the following agents: mumps, LCM, herpes simplex, poliomyelitis, Group B Coxsackie, and appropriate arthropod-borne viruses and leptospira. In 20 per cent of these, sufficient serum remained to permit further tests for encephalomyocarditis, psittacosis-lymphogranuloma venereum, adenovirus infection, toxoplasmosis, fungus infection, infectious mononucleosis and atypical pneumonia.

* Serology for diagnosis of mycotic infection was performed by the Mycology Section, Department of Bacteriology, WRAIR.

† Heterophil agglutination tests were performed by the Department of Serology, WRAIR.

TABLE II

CLINICAL SYNDROMES REPRESENTED IN PATIENTS WITH DISEASE OF THE CENTRAL NERVOUS SYSTEM (1953 TO 1958)

Clinical Syndrome	Total Patients Studied (No.)	Patients with Specific Etiologic Diagnosis	
		No.	Per cent
Aseptic meningitis	430	305	71
Encephalitis	139	100	72
"Paralytic poliomyelitis"	144	116	81

RESULTS

Syndromes. The disease in each of the 713 patients could be classified as aseptic meningitis, encephalitis or "paralytic poliomyelitis." (Table II.) Patients fulfilling Wallgren's criteria [*22*] were classified as having aseptic meningitis. This was the most frequently encountered syndrome in this study (60 per cent of cases) and the most benign. These patients had an acute onset of febrile illness with signs and symptoms of meningeal involvement, pleocytosis and bacteriologically sterile cerebrospinal fluid. Their illness seldom exceeded ten days' duration and all recovered without sequelae.

Patients who presented clinical evidence of more deep-seated neurological involvement were classified as having encephalitis. These patients invariably exhibited various combinations of coma, convulsions, pathological reflexes, mental deterioration, personality changes, tremor and ataxia. Most patients with encephalitis also exhibited meningeal signs (the so-called menigoencephalitis syndrome); however, for this description, these patients were considered to have encephalitis, favoring the more severe signs and symptoms. Similarly, patients with manifest encephalitis who also demonstrated spastic or flaccid paralysis were considered to be in the encephalitis group. There were thirty-nine patients in whom paralysis was a feature of the encephalitis syndrome. Duration of disease in all

TABLE III
SPECIFIC ETIOLOGY OF "VIRAL" CENTRAL NERVOUS SYSTEM SYNDROMES
(1953 TO 1958)

Etiology	Clinical Syndrome			
	Aseptic Meningitis	Encephalitis	Paralytic Poliomyelitis	Total
Mumps	68	22	1*	91
LCM	38	20	0	58
Herpes simplex	6	13	0	19
Leptospirosis†	17	2*	0	19
Poliomyelitis‡	38	5	113	156
Coxsackie‡ A	0	2*	0	2
Coxsackie B	77	2*	1*	80
ECHO‡	51	1*	1*	53
Arthropod-borne viruses§	3	20	0	23
Tuberculosis	1	9	0	10
Other‡	6	4	0	10

* Cases considered atypical and discussed in text.
† Serotypes: L. canicola, eleven; L. pomona, four; L. icterohaemorragiae, three; L. autumnalis, one; and L. pyrogenes, one.
‡ Serotypes and specific agents enumerated in text or Table v.
§ St. Louis encephalitis, seven; Western equine encephalitis, six; Eastern equine encephalitis, two; Colorado tick fever, one; and Japanese encephalitis, seven (all infected in the Far East).

TABLE IV
CLINICAL COURSE OF ENCEPHALITIS
(1953 TO 1958)

Etiology	Total Patients	Outcome		
		Complete Recovery (no.)	Severe Sequelae* (no.)	Death (no.)
Mumps	22	21	1	0
LCM	20	19	1	0
Herpes simplex	13	2	6	5
Arthropod-borne encephalitis†				
Japanese	7	2	3	2
Eastern equine	2	0	1	1
St. Louis	5	4	1	0
Western equine	6	5	1	0

* Residua such as severe paralysis, aphasia, personality changes or mental deterioration.
† Two patients with St. Louis encephalitis and the single patient with Colorado tick fever were classified as having aseptic meningitis and do not appear in this table.

patients with encephalitis frequently exceeded ten days; 10 per cent of patients died during the acute illness, and debilitating sequelae (e.g., severe spastic paralysis, aphasia or mental deterioration) were reported in 15 per cent of cases.

Patients whose illness was characterized by an acute febrile onset, meningeal irritation, pleocytosis and persistent flaccid paralysis, without objective evidence of sensory defect or cortical damage, were considered to have "paralytic poliomyelitis," based on criteria published by the World Health Organization [*24*].

Etiology of Syndromes. Etiologies were established in over 70 per cent of patients with each clinical syndrome (Table II). Aseptic meningitis and encephalitis were of diverse etiology in contrast to the paralytic poliomyelitis syndrome which was almost entirely associated with poliovirus infections. (Table III.) Further, each etiologic agent or family of agents was found to produce disease of diverse clinical manifestations.

At least nine distinct agents or families of agents were implicated in the etiology of the aseptic meningitis syndrome. (Table III.) Group B Coxsackie, mumps, ECHO, LCM and polioviruses and leptospirae were responsible for all but 3 per cent of the diagnoses in this group, and in that order of frequency; however, infection with these same agents also produced encephalitis. Mumps, LCM and herpes simplex viruses were responsible for fifty-five of 100 etiologic diagnoses of encephalitis and actually were as frequently associated with encephalitis as were the arthropod-borne encephalitis viruses.

Certain agents or families of agents had a greater predilection for producing severe disease (*viz.*, encephalitis) than others. Arthropod-borne and herpes simplex viruses gave rise to proportionately more encephalitis than LCM or mumps viruses, even though all four were implicated in the etiology of both aseptic meningitis and encephalitis. Further, these agents caused encephalitis much more frequently than Group B Coxsackie or ECHO viruses or leptospirae.

No essential difference in the clinical course of aseptic meningitis was observed for individual etiologies. In contrast, differences in the clinical course of encephalitis varied significantly with the etiology. (Table IV.) No fatalities resulted from encephalitis due to mumps and LCM viruses, and sequelae were rare; however, death or severe sequelae resulted from 84 per cent (eleven of thirteen) of herpetic encephalitides and 45 per cent of encephalitis due to arthropod-borne viruses. Although the number of patients was small, death and severe sequelae were more common in patients with Japanese and Eastern equine encephalitis than with St. Louis and Western equine encephalitis. (Table IV.) Thus, even among agents which produce encephalitis, variation in the severity of the clinical course of infection was observed.

On clinical grounds, patients with paralysis

could be divided into cases of paralytic poliomyelitis and encephalitis with paralysis. With only three exceptions the paralytic poliomyelitis syndrome was associated with poliovirus infection. On the other hand, encephalitis with paralysis was of multiple etiology (mumps, six; LCM, six; herpes simplex, six; poliomyelitis, four; tuberculosis, two; arthropod-borne virus, one; coccidioides, one; and undiagnosed, twelve). This further justified the separation of paralytic disease into the two groups.

Even though polioviruses were most frequently associated with paralytic poliomyelitis, they frequently caused aseptic meningitis and encephalitis. (Table III.) However, only one of five patients with encephalitis due to poliovirus failed to have concurrent flaccid paralysis.

Ten patients with disease of the central nervous system, eventually established as tuberculous in origin, presented with aseptic meningitis or encephalitis. Tubercle bacilli were recovered from cerebrospinal fluid or central nervous system tissue from each of these patients. The most frequent initial clinical impression in these patients was "viral encephalitis."

Atypical and Miscellaneous Cases. Unusual clinical manifestations of infection were associated with mumps, Coxsackie and ECHO virus and leptospiral infections in ten instances. (Table III.) These patients (three with paralytic poliomyelitis and seven with encephalitis) deserve special comment.

Patients whose disease simulated paralytic poliomyelitis include a two year old girl who had an illness characterized by fever, meningeal irritation and complete paralysis of the right leg. This patient was left with a residual right foot drop. Serum obtained on the seventh and thirtieth days of disease demonstrated an increase in complement fixation antibody titer for mumps from 1:8 to 1:32. Repeated attempts to isolate polioviruses from the stool of this patient or to demonstrate increases in antibodies to polioviruses were negative. The second patient, a thirty-six year old man, survived an acute episode of respiratory embarrassment indistinguishable clinically from bulbar poliomyelitis and was left with residual paralysis of the muscles of the tongue and neck. No isolation specimens were collected but serologic studies showed a significant increase in neutralizing antibody for Coxsackie B-4 virus serotype in the convalescent serum and no detectable increase in poliovirus or other group B Coxsackie virus antibodies. The third case simulating paralytic poliomyelitis occurred in a four year old girl who had a febrile illness with meningeal irritation and paralysis of both lower extremities; bilateral quadriceps weakness persisted during convalescence. Attempts to isolate virus from stool and serologic tests failed to give evidence of recent poliovirus infection. Type 1 ECHO virus was recovered from stool specimens, a significant increase in neutralizing antibody for ECHO 1 virus being demonstrated between the seventh and thirty-first days of disease.

Leptospirosis, although usually clinically benign, was associated with encephalitis in two patients. The infection with L. pyrogenes or a related serotype occurred in a four year old boy in Pennsylvania who presented with meningeal signs, convulsions and abnormal reflexes; he was left with a residual flaccid paralysis of the right leg. Studies for Eastern equine encephalitis, herpes simplex, mumps and polioviruses showed no evidence of concurrent infection with these agents. The case is unique since it was the first reported infection with a strain of this serotype occurring in this country [*23*]. The second patient was a twenty-nine year old man in whom confusion, disorientation and amnesia developed in the course of a central nervous system infection with L. pomona or a serologically related strain.

Two cases of encephalitis associated with Group A Coxsackie virus infections occurred in three year old twin girls infected with type A-2 virus. They suffered simultaneous illnesses of several days' duration characterized in each by apathy, ataxia and asymmetrical deep tendon reflexes. From each patient Coxsackie A-2 strains were recovered from both fecal and throat swab specimens collected during the acute phase of disease; isolation studies for other agents were negative. Both patients' convalescent serums demonstrated a significant increase in complement fixation antibody for the homologous viral isolates and failed to show serologic evidence of recent infection with arthropod-borne, herpes simplex, mumps, poliomyelitis, LCM or Group B Coxsackie viruses, or Leptospirae.

In two patients Group B Coxsackie infections with types B-2 and B-4, respectively, were associated with encephalitis manifested in the first instance (in an adult) by a mild encephalitis with meningeal signs and dorsal plantar reflexes of three days' duration and in the second

(a newborn child) by a fulminating fatal encephalitis and myocarditis. The first case was diagnosed by serologic tests alone (sixteenfold increase in neutralizing antibody to Coxsackie B-2); the second case by isolation of Coxsackie B-4 virus from necropsy specimens. In a single instance an ECHO virus, type 19, was associated with an encephalitis syndrome. This twenty year old man manifested fever, headache, nuchal rigidity, diplopia, nystagmus, bilateral Babinski responses and intention tremor. The laboratory diagnosis in this case was established by recovery of ECHO-19 virus from stool specimens and demonstration of a significant increase in homologous antibody.

The ten miscellaneous cases in Table III represented infections with agents that were less frequently encountered in this study of central nervous system syndromes. These included infectious mononucleosis (three), primary atypical pneumonia (three, cold and Strep. MG agglutinin positive), Rocky Mountain spotted fever (one), histoplasmosis (one) and coccidioidomycosis (two). The patients with infectious mononucleosis did not present with the characteristic clinical features of this disease on admission. In contrast, classic clinical features of the primary disease were apparent in the patients with atypical pneumonia and Rocky Mountain spotted fever, but central nervous system symptoms and signs were sufficiently prominent to warrant diagnostic lumbar puncture which in each instance revealed a predominantly lymphocytic pleocytosis. The patients with histoplasmosis and coccidioidomycosis exhibited CNS symptoms with little or no involvement of other organ systems, so that an initial clinical diagnosis of viral meningitis or encephalitis was entertained.

Serotypes of Enteroviruses. Of the 713 patients in this study, 291 (41 per cent) had infections with enteroviruses.* Further, twenty-one immunologically distinct enteroviruses were implicated. (Table v.) Except for twenty-two patients (six with poliomyelitis and sixteen with Group B Coxsackie virus infections) in whom heterotypic antibody responses to more than one virus were demonstrated [*13*], the specific infecting enterovirus serotype was determined in each patient. All three types of poliovirus were implicated; however, type 1 was more common, being responsible for ninety-five cases while

TABLE V
ENTEROVIRUS SEROTYPES ASSOCIATED WITH DISEASE OF THE CENTRAL NERVOUS SYSTEM
(1953 TO 1958)

Serotype	Cases (total no.*)	Cases with Virus Isolates	
		No.	Per cent
Poliomyelitis Virus (156 Cases)			
I	95	57	60
II	13	5	38
III	42	20	48
Undetermined†	6		
Coxsackie Virus (81 Cases)			
A-2	2	2	
B-2	7	4	57
B-3	23	18	78
B-4	16	13	81‡
B-5	17	14	82‡
Undetermined† (Group B)	16		
ECHO Virus (53 Cases)			
1	1	1	
2	1	1	
4	4	4	
5	1	1	
6	13	13	
6′	1	1	
9	22	8	36
10	1	1	
12	1	1	
14	1	1	
17	1	1	
19	1	1	
JB§	5	5	

* Includes cases established by serology only.

† Cases diagnosed serologically demonstrating antibody increases to more than one serotype of poliomyelitis or group B Coxsackie virus.

‡ One additional patient had both type B-4 and B-5 isolated from stool and had significant antibody increases to both serotypes.

§ Unnumbered ECHO "candidate."

* Poliomyelitis, Coxsackie and ECHO viruses have recently been grouped under the family name of enteroviruses, since all inhabit the alimentary tract and have common properties [*25*]. Over fifty-two serotypes of enteroviruses have been isolated (three poliomyelitis, nineteen Group A Coxsackie; five Group B Coxsackie, and over twenty-five ECHO viruses); however, many of the Group A Coxsackie viruses and ECHO viruses have not been related to disease of the central nervous system in man.

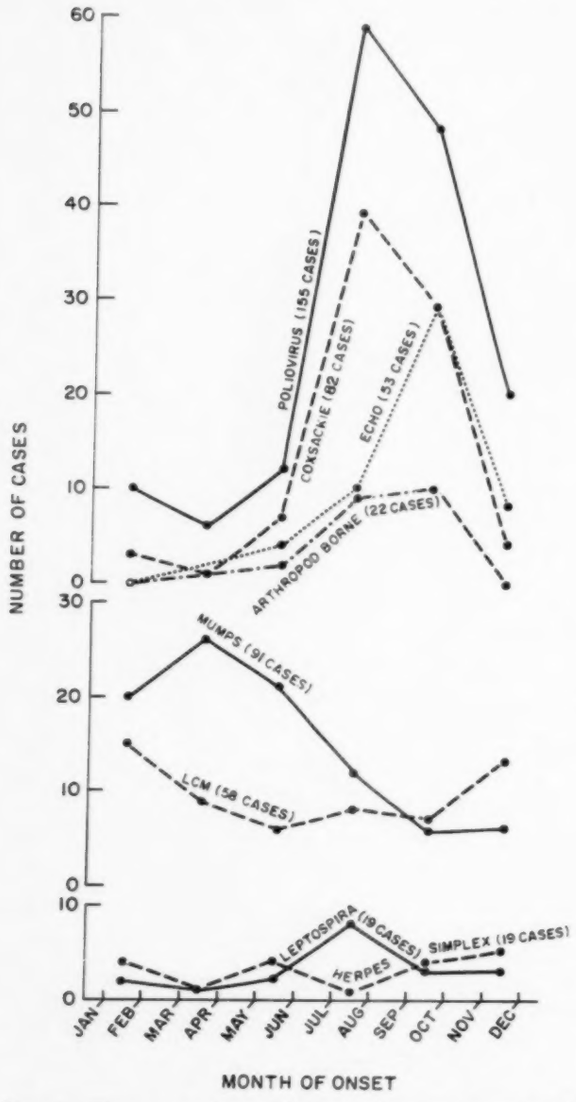


FIG. 1. The seasonal distribution of agents associated with viral disease of the central nervous system, 1953–1958.

types 2 and 3 together accounted for fifty-five. Of the nineteen recognized Group A Coxsackie viruses only one serotype was related to CNS disease during this study. However, all Group B Coxsackie viruses except B-1, and twelve of twenty-five numbered (and one as yet unclassified) ECHO viruses were encountered. (Table v.) Differences in the relative incidence with which various enteroviruses were related to human disease in this study are similar to those described by others [*26,27*].

In 53 per cent of the patients with poliomyelitis, 64 per cent of those with Coxsackie and 74 per cent of those with ECHO virus infections, the specific agent responsible for disease was determined by isolation of virus (generally from stool specimens) as well as significant antibody increase in convalescence. (Table v.) The recovery of more than one enterovirus from stool specimens obtained during the acute phase of disease was rare; however, in one case two viruses (Coxsackie B-4 and B-5) were recovered from the same patient, and serologic study of this patient suggested simultaneous infection with both agents. Early reports suggested that Group A Coxsackie viruses might be encountered frequently as "normal" human intestinal flora [*28,29*], yet none of these were recovered from any of the patients in this study except for the two A-2 strains related to disease. (Table v.) A similar failure to recover Group A Coxsackie viruses as normal flora has also been reported by Kilbourne [*30*].

Isolation of virus from stools of patients failing to demonstrate increases in homologous antibody during disease was rare. Four patients with aseptic meningitis were without significant antibody increase to the ECHO viruses recovered from their stools (one type 4, one type 16, two JB agents). No other etiology for disease was established in these patients, and interestingly, virus (one type 4 and one JB agent) was recovered from cerebrospinal fluid in two. However, because significant increase in antibody was not demonstrated in these patients, they were excluded from this study. Since ECHO viruses were recovered from the spinal fluid of other patients demonstrating increases in antibody to their infecting viruses (three type 4, one type 9, three JB agents), it seems probable that the patients omitted from the study were indeed infected with the viruses recovered from cerebrospinal fluid, and, further, that recovery of a virus from cerebrospinal fluid contributes to the evidence that the agent causes disease of the central nervous system in man [*27,31*].

Seasonal and Annual Variation in Etiologies and Diagnoses. Figure 1 illustrates the seasonal incidence, by month of onset, of eight agents or groups of agents associated with disease of the central nervous system in this study. As expected, poliomyelitis showed a maximum incidence in the summer and fall months; however, poliomyelitis was diagnosed at least once in every month of the year. The seasonal incidence of non-paralytic poliomyelitis corresponded to that of paralytic poliomyelitis. (Table VI.)

TABLE VI

PARALYTIC AND NON-PARALYTIC POLIOMYELITIS BY MONTH OF ONSET (1953 TO 1958)

Syndrome	Jan.–Feb.	Mar.–Apr.	May–June	July–Aug.	Sept.–Oct.	Nov.–Dec.	Total
Paralytic	10	3	10	45	31	13	112
Non-paralytic	0	3	2	14	17	7	43

ECHO and Coxsackie virus infections followed a seasonal distribution similar to poliomyelitis, as befits their common ecological and virological properties. Arthropod-borne virus disease occurred in the warmer months when the arthropod vectors were prevalent. Central nervous system syndromes due to mumps virus showed a distinct seasonal predilection, being prevalent in the spring months, thus following the known seasonal incidence of mumps parotitis; LCM cases occurred somewhat more frequently in the colder months when human contact with wild rodents tends to be greater [*32*]. Herpes simplex virus and leptospiral infections failed to show a clear seasonal predilection.

Of the various etiologies only the enteroviruses showed a significant annual variation in the causation of disease of the central nervous system. Poliovirus infections showed a marked variation in annual incidence. (Fig. 2.) The largest number of poliomyelitis infections diagnosed occurred in 1955, type I poliovirus being the most common serotype implicated in that and all other years except 1957. However, each serotype was encountered in each year of the study.

In 1955 and 1956 type B-3 accounted for over 50 per cent of detected group B Coxsackie virus infections of the central nervous system; however, in 1957, 80 per cent of cases were due to serotypes B-4 and B-5. A similar annual variation was apparent with the ECHO viruses; seventeen of twenty-two ECHO-9 virus infections occurred in 1956 and ten of fourteen ECHO-6 and 6-prime virus infections had their onset in 1955. All ECHO virus cases represented sporadic disease except sixteen ECHO-9 infections which occurred in the European epidemic of 1956 [*33*].

Group B Coxsackie and ECHO viruses were uncommonly encountered during the first two years of this study (1953 and 1954) and poliovirus diagnoses in these years were fewer than would be expected in view of the national incidence [*34*]. During these years specimens for recovery of enteroviruses (i.e., stool, cerebrospinal fluid and throat washings), upon which diagnosis largely depends, were less frequently submitted. Thus the role of these agents in the causation of infections of the central nervous system may actually be greater than reflected by the data in Tables III and VIII.

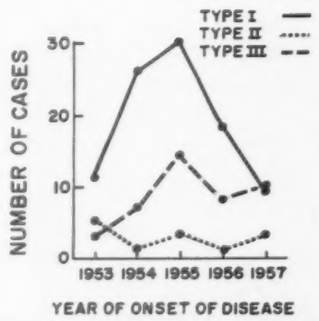


FIG. 2. The year to year variation of poliovirus serotypes in paralytic and non-paralytic disease of the central nervous system.

Table VII summarizes the distribution of the 713 cases by seasons and years of onset with the percentages of successful laboratory diagnoses during each period. Comparable numbers of cases were studied during each of the five years and, with the exception of 1953, little variation occurred in the percentages of positive diagnoses. Almost twice as many cases occurred in the summer and fall as in the winter and spring. Successful diagnoses were most frequently obtained in autumnal and least frequently in springtime illnesses.

COMMENT

The present study is consistent with the general experience that the majority of non-bacterial infections of the central nervous system are of viral etiology; viral infections were associated with 68 per cent of the illnesses of the central nervous system studied. Aseptic meningitis was the most common syndrome (430 of 713 cases);

TABLE VII

DIAGNOSTIC EFFECTIVENESS BY YEAR AND BY SEASON OF ONSET "VIRAL" DISEASE OF THE CENTRAL NERVOUS SYSTEM

(1953 TO 1958)

Season	Year											
	1953		1954		1955		1956		1957		Total Season	
	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.
Winter (Dec., Jan., Feb.)	44	18	62	16	87	31	85	27	86	29	77	121
Spring (Mar., Apr., May)	53	32	70	33	70	23	67	15	56	18	63	121
Summer (June, July, Aug.)	66	32	70	33	68	62	74	74	76	59	72	260
Fall (Sept., Oct., Nov.)	72	29	89	27	77	56	82	62	73	37	79	211
Total by year	60	111	73	109	74	172	78	178	75	143	73	713

NOTE: Per cent = percentage of cases successfully diagnosed.
No. = total number of cases studies.

Group B Coxsackie, mumps, ECHO, LCM and polioviruses were most frequently associated with this syndrome. Encephalitis (139 of 713 cases) was caused by mumps, LCM, arthropod-borne and herpes simplex viruses. "Paralytic poliomyelitis" (144 of 713 cases) was almost entirely associated with poliovirus infections.

Thus the aseptic meningitis and encephalitis syndromes were of diverse etiology, in contrast to paralytic disease. Further, the disease caused by each agent or family of agents was variable, most agents being associated with at least two syndromes. The reasons for these diversities are apparently inherent to man's relationship to the viruses. With the exception of rabies virus, most other agents rarely involve the central nervous system and do so only as a secondary manifestation of systemic disease. Overt involvement of other organ systems is well recognized and often a more common manifestation of infection with such viruses as mumps (parotitis and orchitis), Group B Coxsackie (pleurodynia [*35*] and neonatal myocarditis [*36*]), certain ECHOs (exanthematous disease [*37*]), LCM (respiratory disease [*38*]), and herpes simplex (mucocutaneous lesions and visceral disease [*39*]). Thus the neurotropism of these agents in man is more potential than real. The factors which effect the ultimate localization of viral infection in man are for the most part unknown, but certainly must include those particular to both host and parasite.

Host factors, such as the influence of age, general health and nutrition, may determine to some extent the localization of infection and severity of disease. The nature of acquisition of patients in this study, however, precluded critical evaluation of these factors. On the other hand, the manifestations and clinical course of central nervous system infections definitely varied with different viruses. Certain viruses evoked a wide spectrum of central nervous system symptoms; for example, infection with herpes simplex virus resulted in gradations of severity from benign aseptic meningitis to fulminating, fatal encephalitis. However, certain agents or families of agents were more prone to produce severe disease of the central nervous system than others; for once herpes simplex or arthropod-borne viruses localized in the central nervous system, clinical manifestations of encephalitis most frequently resulted; whereas ECHO and Coxsackie virus involvement of the central nervous system was more frequently manifested as aseptic meningitis. Poliovirus, when producing overt disease of the central nervous system, usually caused typical paralytic disease [*40*].

The difficulties of making an etiologic diagnosis from clinical evaluation of individual pa-

tients is evident. For example, all cases of aseptic meningitis might have been described as "non-paralytic polio," yet only 8.8 per cent of such cases were caused by polioviruses. Furthermore, paralysis associated with signs and symptoms of cortical involvement also might have led to a clinical diagnosis of poliovirus infection; yet LCM, herpes simplex and mumps viruses were all more commonly associated with encephalitis with paralysis than were the polioviruses. Only in the cases of classic lower motor neuron paralysis were polioviruses the most common agent implicated; indeed, with rare exceptions, paralysis in the absence of encephalitic features was virtually pathognomonic of poliovirus infection. The unusual cases of paralysis associated with mumps, Coxsackie and ECHO virus infections and encephalitis associated with leptospirosis and Coxsackie and ECHO virus infections were presented not in an attempt to establish paralytogenic or encephalitogenic properties of these agents but as further evidence of the diverse symptomatology occasionally observed in these infections.

Despite their protein symptomatology, one factor common to all the viral infections of the central nervous system was their acute and febrile nature. All diagnosed infections of the central nervous system in patients in whom chronic inflammatory manifestations developed were due to fungi or M. tuberculosis. The importance of considering M. tuberculosis as a possible etiology early in the clinical course of encephalitis or aseptic meningitis should be evident; for in the present study ten patients with these syndromes, originally considered to be of viral origin, were shown to be infected with M. tuberculosis.

The multiplicity of potential etiologies in any individual patient requires a variety of laboratory studies for diagnosis. This is reflected in the comparison of results on 1,568 cases studied in this laboratory since 1941. (Table VIII.) The first series, summarized by Rasmussen in 1946 [*41*], established the diagnosis of LCM or mumps virus infection in about one-fourth of the cases. During the following six-year period, reported by Adair et al. in 1953 [*42*], two additional agents, herpes simplex virus and leptospira, were studied; however, 75 per cent of cases still remained undiagnosed. In the current five year study of 713 cases, newer technics and more comprehensive application of earlier methods made possible the assignment of a specific etiology to 73 per cent of cases. The earlier studies did not include patients with lower motor neuron type paralysis. Although not strictly comparable, it is clear that the proportion of 26 per cent of cases in this study caused by mumps, LCM, herpes simplex and leptospirae, is in agreement with earlier work.

The increase in etiologic diagnoses in the current five-year study resulted primarily from detection of enterovirus infections; these agents were implicated in 41 per cent of the total patients studied. Enterovirus isolation and serologic studies depend primarily on cell culture technics. (Table I.) For this reason the yearly percentage of cases diagnosed did not climb slowly from 25 to 73 per cent but showed a sharp rise to 60 per cent in 1953 when cell culture methods were first utilized, and increased only moderately thereafter. (Table VII.)

Approximately one-fourth of the cases of "viral" infections of the central nervous system remained undiagnosed. Disease of the central nervous system in man due to the encephalomyocarditis group of viruses [*43*], lymphogranuloma venereum virus [*44*] and Toxoplasma [*45*] has been reported, but none of these agents were associated with disease in this study. The role of herpes zoster-varicella, rubeola, and the many respiratory viruses in disease of the central nervous system is as yet undelineated. Further, non-viral etiologies contribute to cases remaining undiagnosed. Inadequately treated septic meningitis certainly accounts for some of these cases. During this study, but independent of it, specimens from three patients with Hemophilus influenza meningitis partially suppressed by earlier antibiotic therapy were tested prior to their eventual bacteriologic diagnosis. In two other patients an initial clinical diagnosis of paralytic poliomyelitis subsequently was changed to diphtheritic paralysis of the vocal cords in one case and osteomyelitis of the humerus in the other. Brain tumors, septicemia, poisonings and many other causes are listed by Robbins [*46*] as non-viral diseases which must be included in the differential diagnosis of viral infection of the central nervous system.

Etiologic data such as are presented in this study can be correlated with clinical information to formulate an initial etiologic impression in each patient with aseptic meningitis or encephalitis. Apart from the patient's history and the local epidemiologic factors, consideration of the seasonal distribution of various infec-

TABLE VIII

DIAGNOSIS OF "VIRAL" DISEASE OF CENTRAL NERVOUS SYSTEM AT THE WALTER REED ARMY INSTITUTE OF RESEARCH

(1941 TO 1958)

Etiology*	1941–1946 374 Cases (Rasmussen [41])			1947–1952 481 Cases (Adair et al. [42])			1953–1958 713 Cases (Present Study)		
	Positive (no.)	Probable (no.)	Per cent	Positive (no.)	Probable (no.)	Per cent	Positive (no.)	Probable (no.)	Per cent
Mumps	22	35	15	42	17	12	81	10	12.8
LCM	32	10	11	37	7	9	57	1	8.1
Herpes simplex				7†	0	1	17	2	2.7
Leptospirosis				12†	0	3	19	0	2.7
Poliomyelitis							148	8	21.9
Coxsackie A							2	0	0.3
Coxsackie B							78	2	11.2
ECHO							53	0	7.4
Arthropod-borne viruses							23	0	3.2
Tuberculosis							10	0	1.4
Miscellaneous							9	1	1.4
Total diagnosed	54	45	26	98	24	25	497	24	73.1
Undiagnosed	275		74	359		75	192		26.9

* Probable diagnoses include mumps based on sustained antibody titer of 1:64 or greater; LCM based on neutralization indices of 32 and 256 on acute and convalescent serum respectively; herpes simplex based on titer over 1:64, supported in one case by presence of type A inclusions in brain biopsy specimen and in the other case by subsequent eightfold decrease in complement fixation antibody in convalescence; poliomyelitis and Group B Coxsackies based on family contact with proved cases plus isolation of virus or demonstration of antibody to the respective agent; coccidioidomycosis based on significant antibody increase but since complement fixation tests for fungi are not specific [15] result could only be considered diagnostic of a mycotic infection.

† Tests applied consistently only after 1950.

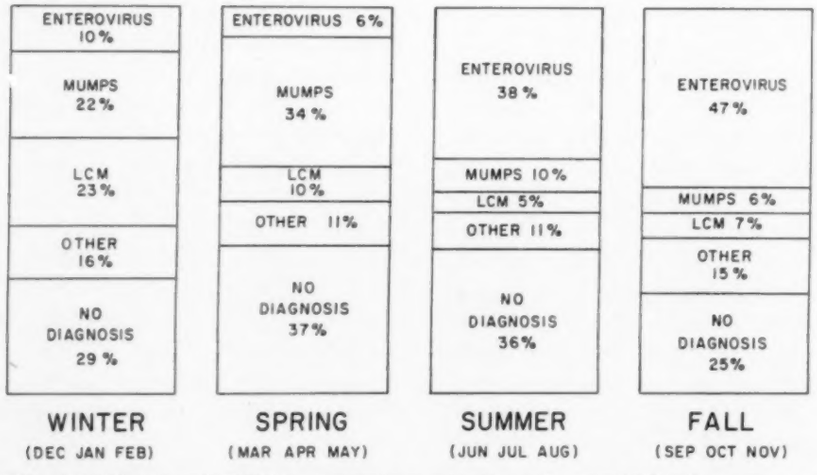


FIG. 3. Etiologic probabilities of aseptic meningitis and encephalitis by season as determined from the patients in this study. Paralytic poliomyelitis is not included since this syndrome is predominately of one etiology.

tious agents provides the best method of venturing an "educated guess" as to the etiologic agent or family of agents causing disease in the individual patient. (Fig. 3.) The generalizations made in Figure 3 do not take into account ecologic and clinical information which would influence etiologic probability. Local outbreaks of mumps parotitis or paralytic poliomyelitis are important considerations in evaluating a case of aseptic meningitis; a tropical climate may facilitate the year around dissemination of enteroviruses [*47,48*] or unusually heavy rainfall may influence mosquito populations and resultant arthropod-borne viral encephalitis; multiple family cases of febrile illness or exposure to persons with pleurodynia or herpetic cutaneous lesions suggest the diagnosis of enterovirus, Group B Coxsackie virus or herpes simplex virus infection in each respective instance; contact with sick dogs or infected animal tissues may suggest leptospirosis and exposure to mice makes LCM virus a more likely etiology of aseptic meningitis or encephalitis.

As in other diseases, all available information must be integrated to develop a rational differential diagnosis directing the immediate management of the patient. Consideration of the data presented may assist in this formulation; however, in most cases, proof of the etiology of aseptic meningitis or encephalitis in the individual patient is dependent upon virologic studies.

SUMMARY

Careful etiologic study of 713 patients with disease of the central nervous system of presumed "viral" etiology related forty immunologically distinct infectious agents to the diseases. Specific etiologic diagnoses were established in 73 per cent of these patients, studied between 1953 and 1958.

Clinically, disease in each patient could be classified as aseptic meningitis, encephalitis or "paralytic poliomyelitis." Aseptic meningitis, a uniformly benign syndrome, was of diverse etiology, associated most frequently with Group B Coxsackie, mumps, ECHO, LCM and poliovirus infections. Encephalitis, which in this series varied in severity, was also of diverse etiology and was caused by many of the same viruses. Mumps, LCM, arthropod-borne and herpes simplex viruses were most often implicated; death and severe sequelae were more frequent in herpes simplex and arthropod-borne virus encephalitides. The paralytic poliomyelitis syndrome (i.e., lower motor neuron paralysis with no evidence of cortical involvement), on the other hand, was due almost entirely to polioviruses.

Enterovirus infections accounted for 41 per cent of all patients studied. Twenty-one different enteroviruses were encountered, although not in equal proportions or constant frequency from year to year. Enterovirus disease, although observed in all months of the year, was more common in late summer and fall. Seasonal variations were also noted for LCM, arthropod-borne and mumps viruses, but probably not for herpes simplex virus or leptospirae. These seasonal variations in virus prevalence were valuable adjuncts to differential etiologic diagnosis in the individual patient.

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Clinicopathologic Conference

Pulmonary Disease and Rapidly Progressive Renal Failure

STENOGRAPHIC reports of weekly clinicopathologic conferences held in the Barnes and Wohl Hospitals, edited by Lillian Recant, M.D. and W. Stanley Hartroft, M.D., are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, a white housewife sixty-six years of age, was admitted to Barnes Hospital for the first time on November 7, 1959, with the chief complaint of cough and weakness of three weeks' duration.

The patient had noted generalized weakness for several months and about three weeks prior to admission a non-productive cough had developed with mild fever, malaise, anorexia and a "head cold." Food did not seem to have any taste, but there was no weight loss. After chest roentgenograms were said to show "a spot on the lung," she was treated with an "antibiotic," dispensed in capsules, over a week's period. No change occurred in either the severity or nature of her symptoms, except for the appearance during the last week before hospitalization of frequent episodes of nocturnal sweating and diffuse aching of the wrists and shoulder joints. There was no history of chills, shortness of breath, hemoptysis or chest pain.

In 1950, the patient underwent an uneventful abdominal operation for "bowel obstruction." The cause of this was unknown; but she remained symptom-free. During the same year her husband died of tuberculosis. She also complained of vague, long-standing "arthritis."

On physical examination the blood pressure was 140/80 mm. Hg, pulse 80, temperature 37.3°C., and the respirations 20. The patient was a well developed white woman, somewhat lethargic, and in no acute distress except for frequent episodes of coughing. Her skin was pale with a slight malar flush. The tongue was slightly smooth and the mucous membranes pale. Arteriolar narrowing was observed in the retinas. A 1 cm. nodule was detected on the right superior pole of the thyroid; the trachea was in the midline; the neck veins were flat. The thorax was symmetrical; auscultation and percussion of the lungs revealed only an increased expiratory phase of respiration in the lower half of the left lung posteriorly. The point of maximal cardiac impulse was in the fifth intercostal space in the anterior axillary line. The rhythm was regular; the first mitral sound was loud; P2 was louder than A2, the latter possessing a tambour-like quality. A sighing grade 2/6 apical systolic murmur, and a grade 2/6 high-pitched, apical, early diastolic murmur of short duration were heard. The abdomen was symmetrically protuberant with the liver dullness extending 3 cm. below the right costal margin. There were no areas of tenderness or any palpable masses. The lower extremities demonstrated varicose veins as well as 3-plus edema, and bone tenderness. All peripheral pulses were palpable. The neurologic examination was within normal limits.

The laboratory data were as follows: The hemoglobin was 9.5 gm. per cent; the packed cell volume 31 per cent, the white blood cell count 19,150/cu. mm. with 88 per cent segmented forms, 3 per cent bands, 5 per cent lymphocytes. The corrected erythrocyte sedimentation rate was 34 mm./hour (Wintrobe method). The urine specific gravity was 1.010, pH 5.5, 2-plus protein, and negative sugar reaction. Many red blood cells and 6 to 8 white blood cells were seen per high power field in the centrifuged urinary sediment. The blood cardiolipin reaction was negative. Two stool examinations were negative both for occult blood and neutral fat. The total serum proteins were 5.2 gm. per cent, with albumin 2.8 gm. per cent and globulin 2.4 gm. per cent; prothrombin time was 48 per cent of normal (repeat value was 100 per cent of normal); normal values were reported for the

protein-bound iodine, thymol turbidity, cephalin cholesterol flocculation, alkaline phosphatase, and the latex agglutination tests. Electrocardiogram was interpreted as follows: sinus bradycardia of 57/minute and right bundle branch block. Roentgenograms of the chest (Fig. 1) were reported as showing left ventricular enlargement, atelectasis of the anterior segment of the lower lobe of the right lung, right pleural effusion, coin lesion on the left (suggesting histoplasmosis), and a diverticulum of the mid-esophagus. A blood culture drawn at the time of admission revealed no growth.

The patient's temperature rose to 38.4°C. on the second hospital day, but fell to 36.2°C. by the next day when distention of the veins on the left side of her neck was noted; she complained of pain in the left shoulder. Her temperature remained below 36.8°C. during the remainder of her hospitalization. A repeat hemoglobin was 8.8 gm. per cent, packed cell volume 28 per cent, red blood cell count 2,930,000/cu. mm., mean corpuscular volume 85 cu. μ, M.C.H.C. 31 per cent. The white blood cell count was 10,150/cu. mm.; the differential was essentially unchanged. The specific gravity of an overnight-collected specimen of urine was found to be 1.010. The urine pH was 4.5 with a trace positive sugar reaction, several red blood cell casts and 4 to 6 red blood cells per high power field. The blood urea nitrogen was 63 mg. per cent and the fasting blood sugar 112 mg. per cent. On November 11 a bronchoscopic examination was within normal limits, and subsequent studies of the bronchial washings were reported as showing normal flora on routine culture, no tumor cells and no evidence of acid-fast bacilli or fungi either on direct smear or appropriate culture. Three sputum examinations for acid-fast bacilli were likewise negative, as was an acid-fast bacillus culture. The skin reaction to both intermediate strength P.P.D. and to Histoplamin was positive, although the degree of responsiveness to each skin test was not recorded.

On November 11, administration of Achromycin® was also begun. Approximately eleven hours after the first dose, swollen, exquisitely tender, hot and painful knees developed with evidence of postpatellar fluid; only the area of the right thumb showed periarticular erythema. These symptoms apparently responded to therapy with analgesics and sedation. However, four hours later, at 3:00 A.M. on November 12, severe "air hunger" developed. The patient did not complain of pain, was oriented and alert, was able to lie flat, but appeared to be terrified. Her blood pressure was 120/40 mm. Hg, pulse 40, and respirations 40. Except for the presence of fine and crackling rales over the lower half of the right lung field, results of the physical examination were unchanged. The veins on the right side of the neck remained flat. Interpretation of the electrocardiogram was as follows: rate 59/minute, question of atrial fibrillation with complete atrioventricular dissociation, a more rapid atrioventricular nodal rhythm in the ventricles and right bundle branch block. The patient was treated for hyperkalemia with a regimen of 10 per cent glucose in water with regular insulin and calcium gluconate added. Isuprel® and Basogel® were also given. Subsequent studies at 4:30 A.M. revealed the blood urea nitrogen to be 97 mg. per cent, blood sugar 142 mg. per cent, sodium 118 mEq./L., chloride 87 mEq./L. and CO_2 13.7 mEq./L. These determinations were repeated on three subsequent occasions during the next twenty hours and showed no significant alterations from the initial values. The blood uric acid

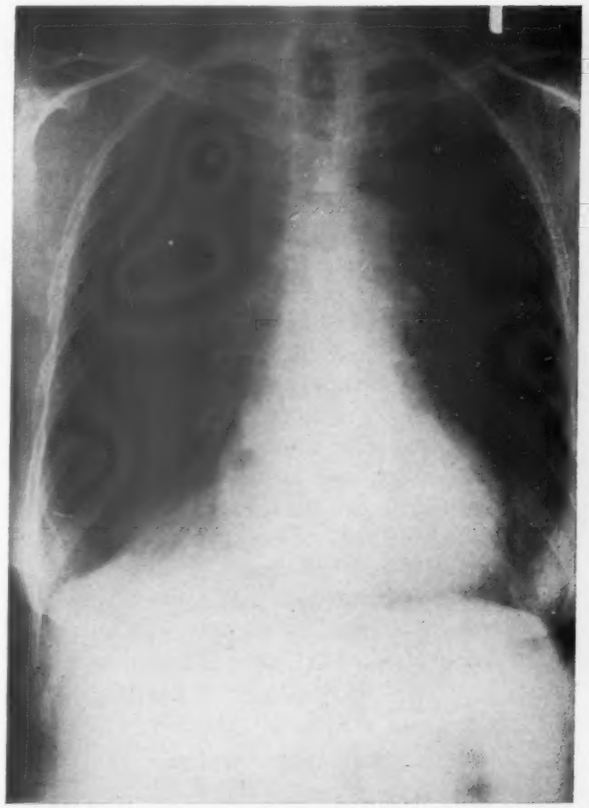


FIG. 1. Roentgenogram of the chest (posteroanterior view) taken on admission.

was found to be 10.5 mg. per cent, calcium 8.6 mg. per cent and phosphorus 10.5 mg. per cent. A venous pressure of 400 mm. of saline was found in the left antecubital vein, together with a Decholin® arm-to-tongue circulation time of twenty-eight seconds. A preparation for the demonstration of lupus erythematosus cells was reported as being negative. By midnight November 12, the patient appeared stronger, brighter and more alert following the intravenous administration of 1,000 cc. of Lactate-Ringers' solution (total of 3,000 cc. of intravenous fluid intake during the previous nineteen hours). The electrocardiogram had now changed so that the rhythm was unclear, being interpreted as atrial flutter (rate 66/minute) with variable atrioventricular response and short periods of atrioventricular dissociation and right bundle branch block. The patient remained in respiratory distress, with fine rales at both bases, despite intravenous digitalization. She died quietly at 5:15 A.M. on November 13, 1959.

CLINICAL DISCUSSION

DR. CARL MOORE: This patient had always considered herself a very healthy woman. The only serious previous illness of which we have knowledge, was an obstruction of her bowel in 1950, relieved by operation. She helped nurse her husband, who died in 1950 of pulmonary tuberculosis. Her present problems developed three to four months prior to admission and could best be classified as follows: (1) pulmonary lesions characterized by consolidation in the upper segment of the lower lobe of the right lung and a coin lesion on the left lung, (2) the possibility of cardiac disease, (3) severe renal disease, and finally (4) distended neck veins on the left side only. The anemia was in all probability secondary to one or several of these manifestations. Dr. Brown, will you discuss the roentgenograms of the chest.

DR. MARK BROWN: A single examination of the chest was made two days after admission. (Fig. 2.) The cardiac contour was somewhat suggestive of left ventricular enlargement. The most striking finding was the area of atelectasis and consolidation in the region of the anterior basilar segment of the lower lobe of the right lung. There was minimal right pleural effusion. The right hilar area was full, but definite lymphadenopathy was not demonstrable. The right superior mediastinum was not widened. There was nothing to explain the elevated venous pressure. The trachea remained midline. The coin lesion mentioned earlier could be seen in the lower part of the left lung field. It had a central area of calcification surrounded by a halo-like area of infiltration. This was a granuloma, probably a histoplasmoma. The lateral projection with barium in the esophagus showed a small mid-esophageal diverticulum.

DR. MOORE: The electrocardiographic changes are pertinent to our discussion, Dr. Massie, would you interpret them?

DR. EDWARD MASSIE: I have chosen two electrocardiographs for presentation. The first showed a normal sinus rhythm with right bundle branch block. The QRS measured almost 0.12 second, and in lead V_1 the typical r r waves were present for the diagnosis of right bundle branch block. The second was representative of the other three electrocardiograms which were taken. No P wave could be seen and, in addition, especially in lead V_2 through lead V_5, the T waves were high and symmetrically peaked. This type of T wave is frequently seen with high blood potassium concentrations. When the blood level reaches 7 mEq./L., the T waves begin to get upright and peaked, and the width of the T wave is often decreased. As this process continues, and the potassium rises to 10 mEq./L. or so, the QRS becomes prolonged. If right bundle branch block had not been present, one would be highly impressed with the degree of prolongation seen in this patient's electrocardiograms. The QRS interval in the second record measured 0.15 second whereas originally it was 0.11 to 0.12 second. With prolonged hyperkalemia, the QRS complex and the T wave almost go together, so that they appear almost as a W complex or a biphasic QRS complex. The other change involves auricular activity: sinus pauses and then sinus arrest followed by auricular inhibition. In such cases the ventricle is driven by the nodal pace maker and subsequently cessation of auricular activity occurs.

DR. MOORE: Dr. Massie, was there any evidence to suggest that this patient had rheumatic heart disease?

DR. MASSIE: The evidence for this diagnosis would have to be derived from the murmurs. This patient was sixty-six years of age. From her past history, there is no reason to assume that she had rheumatic heart disease. She was very sick. Murmurs can appear in acutely ill people, but

diastolic murmurs are not often present unless there is a valvular lesion. It is true that in marked hypertension or in severe anemia dynamic diastolic murmurs are occasionally heard. If the diastolic murmur in this case was confirmed by other observers, then I would have to say that she very likely had some element of valvular disease.

DR. MOORE: Are you in agreement, Dr. Smith?

DR. JOHN SMITH: Yes, but the high-pitched apical diastolic murmur could be due to a fenestration or rent in the valve cusp. This possibility raises the question of infection upon the valve.

DR. MOORE: Do you think this patient was in heart failure?

DR. SMITH: It is difficult to decide because there were so many symptoms and so many apparent causes for all the manifestations of her disease. I am inclined to think that she probably was not in congestive heart failure.

DR. MOORE: Despite the venous pressure of 400, and a circulation time of twenty-eight seconds?

DR. SMITH: I habitually do not trust circulation times. The high venous pressure may have been something else again.

DR. MOORE: In this instance the medical student who made these observations determined the venous pressure on the left side; and you will recall that this woman had distended veins on the left side of her neck. We do not know, and nobody who saw her can remember, whether there was any evidence of distention of the veins of her arm. If there was an obstruction in the left innominate vein, which would cause an obstruction in the left internal jugular, increased venous pressure could have been limited to the left side. These values were interpreted clinically as being evidence of heart failure; it was on this basis that digitalis was given. Could digitalis have contributed in any way, Dr. Massie, to the cardiac arrhythmias which developed?

DR. MASSIE: I do not think so. A venous pressure of 400 mm. is so high that it really suggests a mechanical obstruction rather than heart failure.

DR. MOORE: Dr. Goldman, would you discuss the nature of the two pulmonary lesions.

DR. ALFRED GOLDMAN: The lesion at the base of the left lung, which showed a central calcification, was probably typical of what we call a histoplasmoma. It did not look like an active lesion.

DR. MOORE: Could it have been a carcinoma and still have such a central core of calcium?

DR. GOLDMAN: Calcification can occur in tumors, but it is rather typical of a histoplasmoma. It could also be a tuberculoma. The lesion at the base of the right lung looked like atelectasis of the anterior segment of the lower lobe of the right lung. This segment can be obstructed from many causes. Of course, the first one to consider would be an intrinsic obstruction, like an adenoma. Such a lesion could have been present for many years without producing too many symptoms. Carcinoma can certainly produce an intrinsic stricture. Tuberculosis might produce the same. In this patient the lesion did not look like infarction or pneumonia because it was so well defined; however, it cannot be ruled out. We would have to think first of an intrinsic obstruction. If there were associated mediastinal lesions, we would suspect bronchogenic carcinoma which could play a part in the obstruction of the veins in the left neck. The catch here is that there did not seem to be anything in the mediastinum.

DR. MOORE: Could there have been a lesion producing obstruction of the left innominate vein which was too small to be seen in the roentgenogram.

DR. GOLDMAN: That certainly was possible.

DR. MOORE: If you assume that there is such an obstruction, then must you also assume that it probably is a metastatic lesion from the lung, or from the bronchus? Or could tuberculosis do this?

DR. GOLDMAN: A mediastinitis due to tuberculosis can produce obstruction of vessels, but I doubt that this was tuberculosis. All we really can say is that there was an area of atelectasis involving the anterior segment of the lower lobe of the right lung and one of the most common causes for atelectasis would be a lesion in that bronchus. There was nothing else to suggest carcinoma and no lesions were seen which could be responsible for producing distention of the veins in the left neck.

DR. MOORE: This woman had no manifestations at the time of her admission to suggest renal disease, except for the presence of microscopic hematuria. Dr. Bricker, you have probably talked to the medical student who made the last urinalysis. He said the red cell casts looked perfectly characteristic to him, but took the trouble to look up two house officers who confirmed the fact that he had truly found red

blood cell casts. This observation is an important one.

DR. NEAL BRICKER: It certainly is. However, we are somewhat handicapped in that we are permitted only a brief look at this renal disease at an unknown point in its natural history. We have no indication as to its date of onset or its chronicity. Thus we do not know whether this was the end stage of a chronic lesion or a fulminating form of acute renal failure. We do have some data, however, which I would like to summarize. We know that the woman had a blood urea nitrogen of 63 mg. per cent shortly after admission, and within a relatively brief interval, the value increased to 97 mg. per cent. We also know that in association with the increasing azotimia she was oliguric, and that she had hyperkalemia, acidosis, hyperphosphatemia with attendant hypocalcemia, hyperuricemia and a markedly depressed serum sodium concentration. The fact that her initial blood urea nitrogen was 63 mg. per cent suggests that she had a renal lesion before admission to the hospital, but how long before, we do not know.

One might characterize the renal lesion as follows: (1) It was certainly diffuse and involved both kidneys. (2) It was severe. (3) It was associated with a marked decrease in the population of functioning nephrons. (4) Those nephrons that continued to function, presumably were involved with what we may call, an active glomerulitis. It is in the latter regard that the red cell casts become of extreme importance. Supporting evidence for glomerulitis is also provided by the fact that proteinuria was noted on each urinalysis, and that striking hematuria was observed on the initial urinalysis.

In setting up a differential diagnosis, we must first focus our attention upon intrinsic renal lesions which will produce glomerulitis, massive destruction of nephrons and a rapidly downhill course. Then we must attempt to correlate the lesion with the extrarenal abnormalities. I would like simply to list three or four possibilities: The first one, which I know you have thought about in some detail, is a necrotizing angiitis. The second is systemic lupus, or a closely allied disease of the connective tissue. The third is glomerulonephritis, for which we have no ancillary evidence. The fourth is bilateral thrombosis of the renal veins. If the patient did have a carcinoma of the bronchus and a thrombosis in her innominate vein, which reflected a generalized thrombophilic tendency, this last possibility might receive some support; however, the red cell casts are somewhat unusual in thrombosis of the renal veins. Other possibilities seem unlikely but I shall mention them for completeness sake. Amyloidosis produces predominant glomerular involvement, and could appear in a woman with a history of a gastrointestinal lesion in 1950, and a pulmonary lesion of unknown duration; here, too, the red cell casts would be distinctly unusual, as would the fulminating course. Lastly, pyelonephritis, tuberculosis and histoplasmosis can be excluded as a cause of her progressive renal failure, although without information regarding the bacteriology of her urine, the gross architecture of her renal medulla and pelvis, or indeed even the size of her kidneys, one cannot exclude the possible coexistence of these diseases.

DR. MOORE: Subacute bacterial endocarditis?

DR. BRICKER: I should have mentioned that. Yes, the renal lesion of subacute bacterial endocarditis can present either as an acute diffuse glomerulonephritis or as a focal lesion and could give this clinical picture.

DR. MOORE: Dr. Smith mentioned earlier the possibility of subacute bacterial endocarditis. We have only one negative blood culture. Do you think this diagnosis seriously needs to be considered, Dr. Smith?

DR. SMITH: I rather thought of it as an outside possibility and as a means of explaining the murmur.

DR. MOORE: Dr. Harford, one cannot read this chart without being impressed that the arthritis or arthralgia developed while the patient was taking an antibiotic—we do not know which one. She came into the hospital with renal involvement, with red cells in her urine; then after several days without antibiotics, she was given acromycin. Within eleven hours an acute change occurred. She became very apprehensive and had a sense of impending death even though she was a passive and stoical person. Acute joint manifestation and air hunger developed. These reactions certainly suggest the possibility of a hypersensitivity reaction to the acromycin.

DR. CARL HARFORD: Tetracycline is an extremely uncommon cause of hypersensitivity. However, in Dr. Alexander's book* there is a description of a patient who ingested 1 gm. of chlortetracycline and ten minutes later had

* ALEXANDER, H. L. Reactions with Drug Therapy, p. 106. Philadelphia. 1955. W. B. Saunders Co.

severe dyspnea. In the present patient, dyspnea occurred eleven hours after ingestion of the drug so that the possibility of a causal relationship seems less definite. If the dyspnea was a reaction of hypersensitivity, the patient would need to have been sensitized by a previous drug, because reactions of hypersensitivity usually occur ten or more days after the initial exposure. I was inclined to discount the possibility of the dyspnea being caused by a member of the tetracycline group for these reasons. On the other hand, she did receive some kind of antibiotic or similar drug before she entered the hospital. Sulfonamide drugs characteristically produce this type of picture, and I think need to be considered seriously in this case. One cannot go beyond that. I should like to comment on the possibility of subacute bacterial endocarditis.

DR. MOORE: Before you do, may I ask one other thing? The patient was given tetracycline when her urinary excretion was very low, so that by the time she received two doses, she probably had a high blood level of tetracycline. Would this make any difference in your interpretation?

DR. HARFORD: Yes. A decreased urinary excretion of the drug would probably result in higher blood levels and render the likelihood of a reaction to the drug somewhat greater.

DR. MOORE: Do you care to make a comment about subacute bacterial endocarditis now?

DR. HARFORD: Despite the fact that the blood culture was negative, some of the symptoms do tie in with subacute bacterial endocarditis: murmur, anemia, hematuria, low grade fever and arthritis.

DR. MOORE: Is it not extremely rare to have this degree of renal insufficiency with glomerulitis of subacute bacterial endocarditis?

DR. HARFORD: Severe renal insufficiency is not common but it does occur in patients who have had the disease over a long period of time. However, under these circumstances the blood cultures are usually positive, so your point is well taken. I would agree with Dr. Bricker that we may suspect that this patient had some preceding renal involvement.

DR. OLIVER ABEL: It may be of interest to point out an article in the May 1959 issue of the *Annals of Internal Medicine** in which the authors mention three phenomena which may occur following tetracycline therapy: (1) an exacerbation of known lupus, (2) a lupus-like picture, or (3) the development of a positive L.E. preparation without symptoms.

DR. MOORE: Dr. Smith, do you have any further comments about the possibility of a drug-induced necrotizing angiitis?

DR. SMITH: None, except that I considered it a definite possibility. May I have a moment to explain my interpretation of the heart lesion? The heart appeared enlarged on the x-ray film. With a diastolic murmur such as was heard, one would anticipate left ventricular hypertrophy; even if the lesion had been of very short duration, since cardiac hypertrophy may occur very rapidly. To me there seemed to be, as I analyzed your earlier question, insufficient pulmonary signs and peripheral edema to make me think that a serious grade of heart failure was present. It is difficult to use the circulation time well. Often, one cannot be certain that the bolus of material introduced into a vein follows an axial venous stream, and is therefore being conveyed with maximum rapidity to the heart. There have been instances in which the circulation time was found to be prolonged when there was no reason to believe that congestive heart failure existed. This patient did have heart disease. There probably was an element of congestive heart failure from the beginning.

DR. SEYMOUR REICHLIN: The cardiac findings are very peculiar. The description here of an early diastolic murmur heard at the apex, with a tambour quality second aortic sound, despite normal blood pressure, suggests a disease of the aortic valve.

DR. MOORE: I do not believe that anyone could possibly approach a final diagnosis here with any degree of assurance or conviction. One can make a perfectly logical explanation for what happened by suggesting, as Dr. Goldman did, that this woman had a coin lesion probably related to histoplasmosis, or to tuberculosis. This lesion had nothing to do with her terminal illness. She also had a bronchogenic carcinoma with mediastinal invasion and partial obstruction of the left innominate vein. Finally, her renal lesion was on the basis of a glomerulitis, produced by drug hypersensitivity leading to an angiitis. I doubt very much whether that is the correct answer, but at least it is plausible.

PATHOLOGIC DISCUSSION

DR. JOSEPH WILLIAMSON: The appearance of this patient at autopsy was that of a well devel-

* DOMZ, C. A., MCNAMARA, D. H. and HOLZAPFEL, H. F. Tetracycline provocation in lupus erythematosus. *Ann. Int. Med.*, 50: 1217, 1959.



FIG. 2. Gross photograph of a firm, hemorrhagic area of the lower lobe of the right lung which is lobular in distribution.



FIG. 3. Gross photograph of a kidney. The surface is granular and contains scattered petechiae, seen as tiny black dots. The cortex is not thinned.

oped, well nourished woman. External examination was non-contributory except for the presence of a healed mid-line surgical incision in the anterior abdominal wall. The heart weighed 400 gm., which represented a moderate degree of enlargement, and as Dr. Smith suggested, a large fenestration was present on the right anterior cusp of the aortic valve, probably accounting for the aortic murmur. A 1 cm. annular area of fibrosis was present in the outflow tract of the left ventricle about 1.5 cm. proximal to the valve, and was thought to represent a "diastolic pocket" characteristic of aortic regurgitation.

The lungs weighed 1,250 gm., which is approximately twice the normal weight. They were firm to palpation and several 1 to 2 cm. poorly defined nodules were scattered through all lobes, but a calcified nodule corresponding to the coin lesion seen on the roentgenogram was not found. The cut surfaces were moderately congested, particularly the lower lobe of the right lung, and considerable amounts of fluid were expressed with ease from the cut surfaces. The cut surfaces of the nodules were yellow-white in color, and had a distinct granularity. In the lower lobe of the right lung, a sharply circumscribed hemorrhagic area of consolidation about 5 cm. in diameter was present. (Fig. 2.) It was very firm and had a granular appearance. Beneath this area the diaphragm was adherent to the pleura, and between the pleura and the diaphragm was yellow-white firm tissue.

The kidneys were of normal size, soft and flabby. The capsules were quite adherent, and when removed revealed moderately granular cortical surfaces. (Fig. 3.) The cut surfaces were moderately congested and numerous small white punctate areas could be seen scattered throughout the cortex, probably representing enlarged, bloodless glomeruli. Both knee joints were opened, and each contained approximately 10 to 15 cc. of an opalescent, stringy, mucinous fluid, which on gram-stained smears contained numerous polymorphonuclear leukocytes but no organisms.

DR. ROBERT M. O'NEAL: Microscopically, the lungs were quite diseased, with an even greater extent of pathologic change than had been suspected from gross examination. Throughout large areas of the lungs, there was massive hemorrhage into alveoli which contained fibrin,

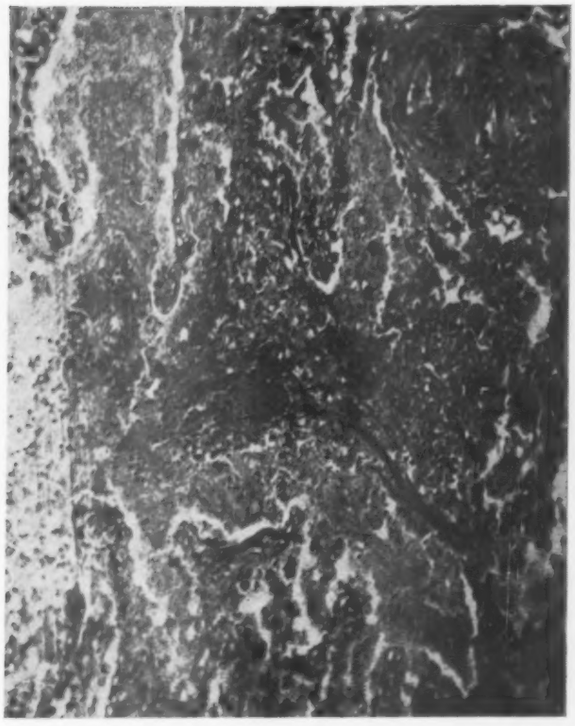


FIG. 4. As area of lung with necrosis of tissue and fibrin deposition in the center of the field. Air spaces contain fibrin and red blood cells. Hematoxylin and eosin stain, magnification × 100.

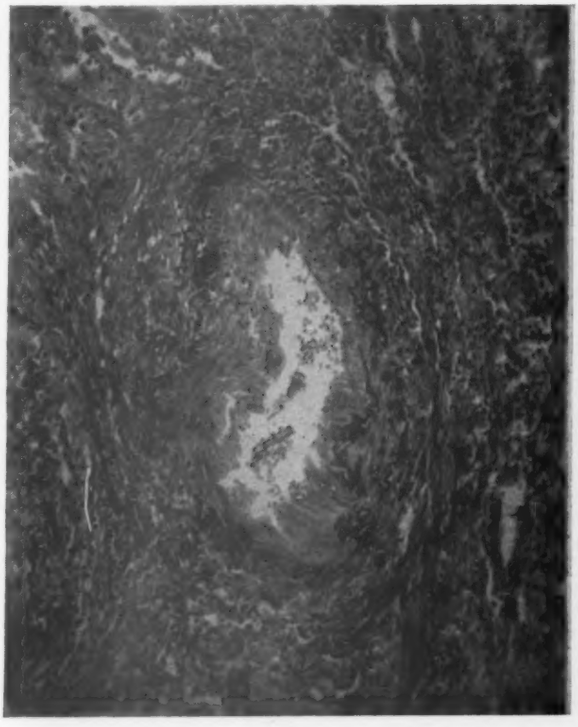


FIG. 5. A medium-sized pulmonary artery lying in an area of dense scar. The muscular wall has been partly destroyed, and the elastica is broken and in disarray, indicative of a healing arteritis. Aldehyde-fuchsin–van Gieson–hematoxylin stain, magnification × 100.

red blood cells and edema fluid. In the areas of intra-alveolar hemorrhage (Fig. 4) there were focal areas of necrosis of alveolar walls. Necrosis of alveolar walls is not consistent with what has been called "uremic pneumonitis," and therefore these changes are more than simply the effects of uremia with extravasation of blood into air spaces.

Over the more discreet pulmonary lesions observed grossly some fibrosis of the pleura was present, indicating they had been there for some time. Such areas, with marked fibrosis, fairly well demarcated and rather lobular in distribution, could have produced a configuration similar to the coin lesion seen on the roentgenogram, but no calcification was observed microscopically. In these fibrotic, older lesions numerous blood vessels could be seen entering the area, but the normal pattern of air spaces had been completely destroyed. With hematoxylin and eosin staining, the remnants of some vessels, completely filled with old organized thrombi, were barely visible. With aldehyde-fuchsin staining, actual destruction of the walls of some of the blood vessels was apparent; the elastic walls were fragmented in many places, the vessels lying within dense scar. (Fig. 5.) In some of the areas in which there was dense scar, in the medial segment of the lower lobe of the right lung, there were focal areas of recent necrosis. These foci had the hazy blue appearance characteristic of scattered nuclear material, and many multinucleated giant cells were scattered through the scar nearby. (Fig. 6.) At first impression this resembled an infectious granuloma such as tuberculosis; there were necroses and many giant cells. But no organisms were demonstrable on acid-fast or periodic acid-Schiff staining. On aldehyde-fuchsin staining of these areas, where there were quite a few giant cells, we noticed fragments of elastic tissue that appeared to be being engulfed by the giant cells. Fragmentation of elastic tissue is sometimes accompanied by a giant cell response, and therefore the presence of fragmented elastica is a possible explanation for the presence of giant cells in this case. Regardless of the pathogenesis of these focal pulmonary lesions, they are best classified as necrotizing arteritis with granuloma formation.

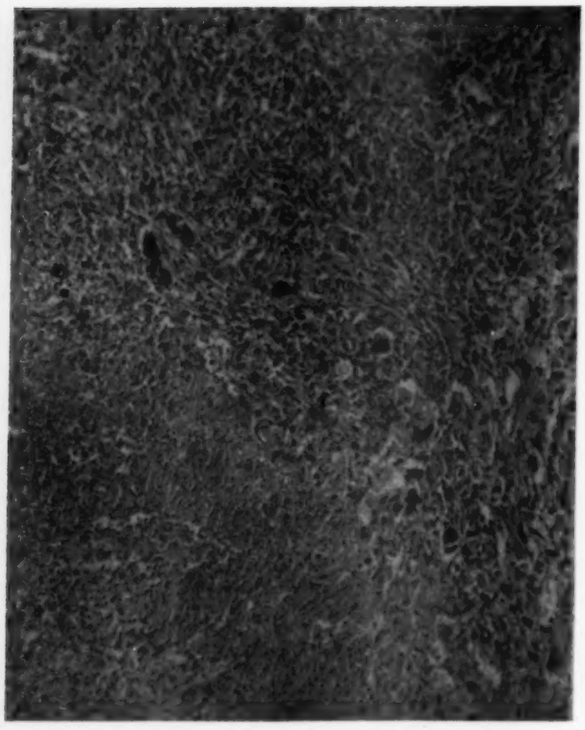


FIG. 6. A focus of necrosis (lower left) in a scarred area of the lung, with numerous giant cells at the periphery giving the characteristic granulomatous appearance. Hematoxylin and eosin stain, magnification × 100.

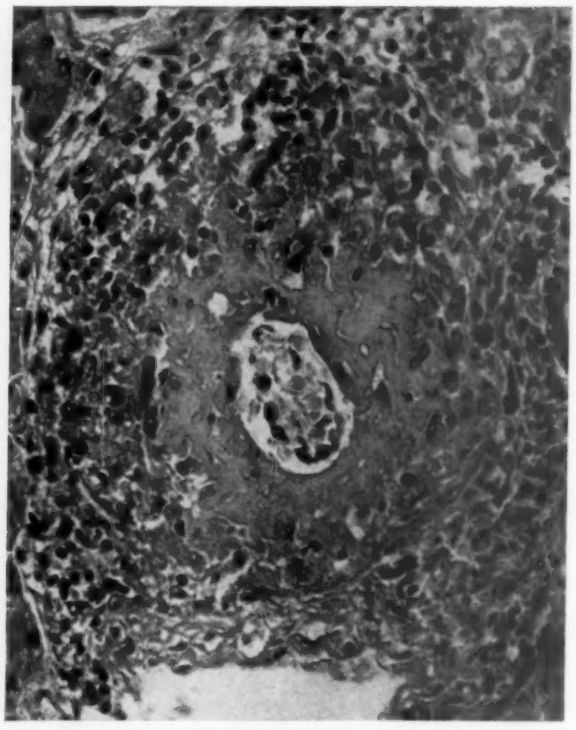


FIG. 7. A necrotic small artery in an hepatic portal space. The smooth muscle wall has been completely replaced by "fibrinoid," appearing here as grey, slightly fibrillar, material. Most of the cells about the vessel are the normal lymphocytic population of a portal space. Hematoxylin and eosin stain, magnification × 300.

Throughout other organs, especially spleen, liver and kidneys, there were scattered early necrotizing lesions of small muscular arteries. (Fig. 7.) Inflammatory reaction about these small arteries and arterioles was scant or absent, but the muscular walls were replaced by fibrinoid material characteristic of the hypersensitivity type of necrotizing angiitis.*

The kidneys were symmetrically and diffusely involved, just as Dr. Bricker suggested that they would be. Every glomerulus showed proliferation of the epithelial cells (Fig. 8) and there were numerous necrotic glomerular tufts throughout all areas. Occasional arterioles showed necrosis of their walls (Fig. 9), while others showed only dense hyalinization. How much of the granularity of the renal cortical surface was present in this older woman before this disease started is impossible to say. The microscopic picture is compatible with some degree of long-standing arteriolar nephrosclerosis. However, the principal renal disease present at autopsy anatomically was glomerular, and if the kidneys were considered alone the morphologic diagnosis would be subacute glomerulonephritis with malignant nephrosclerosis; that is, with necrosis of arterioles.

In the heart there were little patchy areas where the muscle fibers had been lost and replaced with granulation tissue. This was not extensive, and the muscle loss probably was insufficient to account for the clinical heart failure. This focal necrosis of myocardium is probably due to the necrotizing angiitis, with involvement of small blood vessels.

Beneath the synovial lining of the right knee joint there was early necrosis of some of the small arteries surrounded by collections of polymorphonuclear leukocytes. Over the synovial lining there was a fibrinous exudate, also containing polymorphonuclear leukocytes. No organisms were present in this area, and I would interpret the synovial lesion, as the myocardial disease, as local damage secondary to arteritis and vascular occlusion.

* ZEEK, P. M. Periarteritis nodosa and other forms of necrotizing angiitis. *New England J. Med.*, 248: 764, 1953.

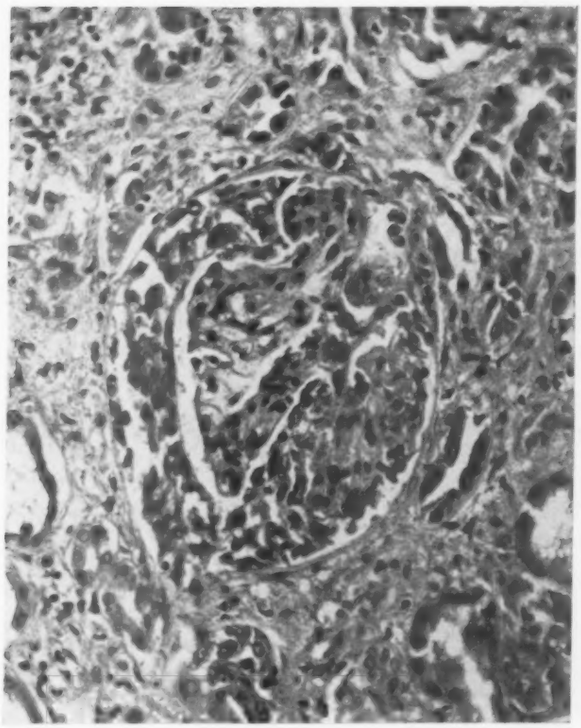


FIG. 8. A glomerulus representing a common lesion in the kidneys of this patient. To the left of the glomerular tuft, there is marked epithelial proliferation forming a crescent between the tuft and Bowman's membrane. This is the characteristic lesion of subacute glomerulonephritis. Hematoxylin and eosin stain, magnification × 300.

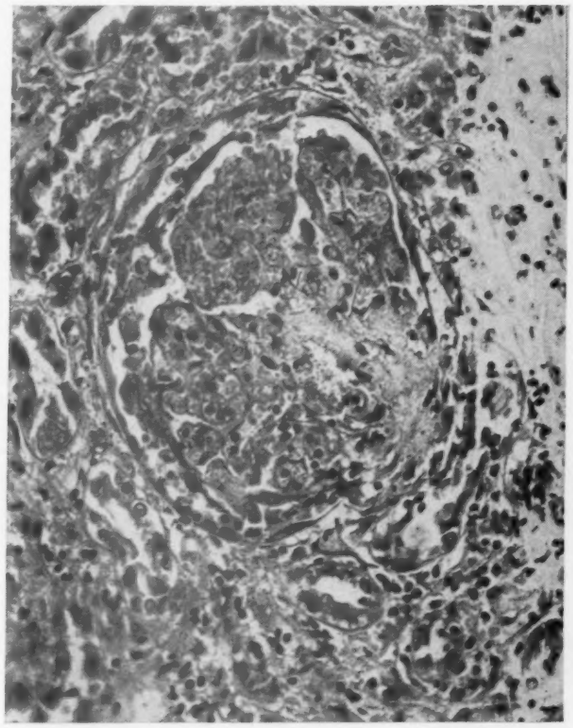


FIG. 9. Another glomerulus showing early crescent formation but in addition necrosis of the wall of the arteriole at the glomerular hilus. Many glomerular tufts were also necrotic. Hematoxylin and eosin stain, magnification × 300.

This case, then, fits very nicely with the triad that has been described for Wegener's granulomatosis. The patient had necrotizing angiitis, she had subacute glomerulonephritis and she had granulomatous lesions of the respiratory tract, each quite classic from a morphologic standpoint.*

The final anatomic diagnoses were: Wegener's granulomatosis characterized by multiple necrotizing granulomas with giant cell reaction in the lung, subacute necrotizing glomerulonephritis, widespread necrotizing angiitis with involvement of small muscular arteries in the lungs, kidneys, liver, spleen, ovary, synovia of both knees, heart (with focal necrosis of myocardium) and diaphragm (with acute myositis) and fibrinous and hemorrhagic pneumonitis of right lung, most advanced in the lower lobe; subacute laryngitis with superficial ulceration (history of bronchoscopy, two days); congestion of the mucosa of the gastrointestinal tract and urinary bladder, slight; petechiae in the mucosa of the renal pelvis; follicular hyperplasia of the spleen, marked; arteriosclerosis of the aorta and coronary arteries, slight; hypertrophy of the heart, 400 gm.; fenestration of the right anterior aortic valve cusp with annular area of fibrosis of endocardium inferior to the right anterior aortic valve cusp (diastolic pocket) (history of aortic diastolic murmur); sessile fibrous polymorphonuclear leukocytes of the gastric mucosa, 1 cm.; Multiple leiomyomata of the uterus; Endometrial polyps (two); 20 cm. healed right paramedial incision in the anterior abdominal wall, and dense fibrous adhesions of the peritoneum (history of abdominal surgery, type unknown); varicose veins, moderate; nodular thyroid.

* GODMAN, G. C. and CHURG, J. Wegener's granulomatosis. *Arch. Path.*, 58: 533, 1954.

Case Reports

Lethal Congenital Neutropenia with Eosinophilia Occurring in Two Siblings*

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THIS report deals with a lethal congenital neutropenic syndrome which differs in certain respects from those heretofore recorded. It was observed in two infant siblings of opposite sex born six years apart to healthy parents of Anglo-Saxon descent. There are five older siblings, a girl and four boys, all in good health. There is no known degree of parental consanguinity.

CASE REPORTS

CASE I. T. P. (No. A-204–52), a male infant, was delivered spontaneously after an uneventful full term pregnancy. The birth weight was not recorded. No abnormalities were noted initially. At the age of seven days, three furuncles appeared on the left lower eyelid, one of which persisted despite penicillin therapy. At the age of fourteen days, a red, tender hot swelling arose in the left side of the neck near the angle of the jaw. During the next two weeks the swelling increased in size and a temperature of 103°F. developed. A suppurative lesion appeared on the right thumb. At the age of one month the infant was hospitalized for treatment of these lesions. Upon failure of the cervical inflammatory mass to respond to penicillin therapy, it was incised, drained and a biopsy was performed. Staphylococcus aureus grew on cultures. Biopsy showed coagulation necrosis of tissue with a surrounding zone of infiltration of lymphocytes and plasmocytes which contained remarkably few neutrophils. The urinalysis revealed no abnormalities. The patient was discharged improved.

At the age of seven weeks he was rehospitalized with clinical evidence of severe tracheobronchitis and severe pustular dermatitis of the face. Evidence of infiltration of the right mid-lung field appeared in the roentgenogram. Febrile agglutinins were negative.

Otitis media occurred at the age of four months, requiring hospitalization.

Upon final admission, at the age of five months, the infant was critically ill with bilateral ostitis media, widespread furunculosis, and a distended abdomen. Blood culture revealed Pseudomonas aeruginosa. Serum protein determinations were reported as follows: total protein, 4.8 gm. per cent; albumin, 2.6 gm. per cent; globulin, 2.2 gm. per cent. The patient died fifteen days after admission. Terminally, neutrophils had disappeared completely from the peripheral blood. The hematologic findings are summarized in Table I.

Examination at autopsy disclosed multiple subcutaneous abscesses at the sites of injection, characterized by a cellular reaction limited to lymphocytes, monocyte forms, and a minimal to moderate number of plasmocytes. No neutrophils were identified. Sections of the marrow revealed a high degree of cellularity, with a minimal amount of fat. Lymphocytes comprised about a half of the cell population, the remainder being divided about equally between eosinophils in all stages of maturation, monocytoid cells and erythrocyte precursors. No members of the neutrophil series were recognized. Megakaryocytes appeared in normal numbers. There was a scattering of plasmocytes; their numbers were not increased. No other major abnormalities were evident, grossly or upon microscopic examination. There were no histologic features of leukemia, histiocytosis, any of the storage diseases, or histoplasmosis.

CASE II. D. P. (No. A-125–58), a female infant, was born six years later to the same parents after a similar uneventful full term pregnancy and delivery. There had been no intervening pregnancy. The infant weighed 8 pounds, 4½ ounces and appeared normal at birth. At the age of three days a pustular dermatitis, resembling impetigo developed, which persisted despite penicillin therapy. She was hospitalized at the age of two months because of persistence and spread of her impetigo-like pustular dermatitis. She seemed emaciated, and her color was poor. Rhonchi and wheezes were audible throughout the chest. Roentgenogram of the chest indicated the presence of an infiltrate at the right hilus. The urinalysis was within normal limits. A serum protein electrophoretic pattern was run on the same filter paper strip with a normal

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TABLE I

PERIPHERAL BLOOD HEMOGRAMS

Data	Hemoglobin (gm. %)	Color Index	White Blood Cells (per cu. mm.)	Segmented Forms (%)	Stab Forms (%)	Eosinophils (%)	Basophils (%)	Lymphocytes (%)	Monocytes (%)	Other
Thomas P.										
Born 2/6/52										
3/11/52	11.2	1.0	20,400	2	6	7	0	57	3	25U*
3/26/52	...	...	16,100	5	0	0	3	45	43	4S*
4/11/52	12.8	1.0	8,700	1	3	8	0	48	40	...
5/30/52	10.5	1.0	10,500	2	0	8	0	62	5	...
7/8/52	8.5	0.9	19,100	0	0	0	0	78	2	20U*
Died, 7/25/52										
Dorothy P.										
Born, 5/19/58										
5/22/58	28	1.2	11,200	14	0	10	0	64	12	...
7/29/58	13	0.9	20,000	1	0	4	0	80	13	...
8/2/58	...	...	15,000	0	0	6	0	75	19	...
Died, 9/20/58										

NOTE: Platelets appeared adequate in numbers and normal in morphology in all blood films.
* U: Unidentified, S: Stem cells.

control. Visual comparison of the two patterns showed no outstanding differences, except for a minimal increase in the beta and gamma components of the patient's protein pattern.

At the age of four months, the infant was readmitted to the hospital for the last time with a temperature of 103°F., widespread pustular dermatitis, and an umbilical draining sinus that had been present for three weeks. Coagulase-positive staphylococci were cultured from the sinus, which proved to originate in an infected urachal cyst. The cyst was excised. The patient died on the first postoperative day. Hematologic findings, summarized in Table I, are characterized by a total absence of neutrophils from the peripheral blood. Coagulase-positive Staph. aureus and Klebsiella pneumoniae grew on blood cultures taken at autopsy. Fungus cultures of lung, liver and spleen were negative.

The anatomical findings at autopsy were essentially identical with those of the male sibling who died six years before. Grossly, except for the site of excision, there were no abnormalities. There was no enlargement of the liver or spleen. About the site of the excised urachal cyst there was an abundant infiltrate of lymphocytes and monocytes, a scattering of plasmocytes, and a complete absence of polymorphonuclear neutrophils. The spleen and lymph nodes were histologically non-contributory. Marrow sections were highly cellular and, as in the previous case, dominated by lymphocytes associated with large numbers of monocytoid cells and eosinophils. Erythrocyte precursors and megakaryocytes appeared to be present in normal numbers. Marrow smears (Fig. 1) and imprints of good quality were obtained at autopsy. A marrow differential count (Table II) confirmed the histologic impression of relative cell numbers, including the virtual absence of neutrophils and neutrophil precursors.

COMMENTS

During the past fifteen years there have emerged into medical consciousness a number of new syndromes, dysgammaglobulinemias and neutropenias, congenital and acquired, for the most part occurring as primary disorders with hypersusceptibility to infection a common clinical manifestation. Their recognition is partly a by-product of the antibiotic era in that

TABLE II

MARROW DIFFERENTIAL COUNT IN CASE II
(PER 1,000 CELLS)

Myeloblasts	55
Promyelocytes	16
Neutrophilic myelocytes	2
Neutrophilic metamyelocytes	0
Neutrophilic mature	0
Eosinophilic myelocytes	30
Eosinophilic metamyelocytes	55
Eosinophilic mature	86
Basophilic myelocytes	2
Megakaryocytes	0
Monocytes	12
Reticulum cells	92
Plasma cells	20
Lymphocytes	553
Pronormoblasts	7
Normoblasts	80
	1,000

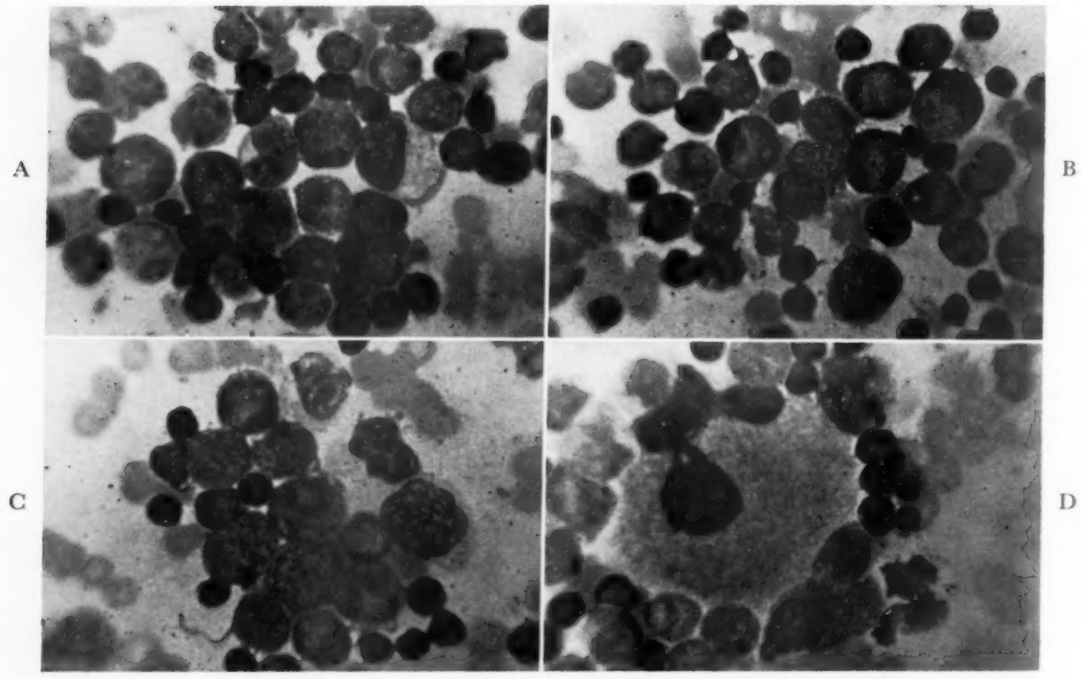


FIG. 1. Case II. Marrow Smears: A, monocytoid cells and lymphocytes; B, eosinophilic myelocytes, metamyelocytes, segmented cells; C, plasmocytes, stem cells, promyelocytes, eosinophilic series; and D, megakaryocyte; normoblasts. Wright's stain. Original magnification × 950.

affected persons who are now able to endure a long enough sequence of severe infections to attract attention to the abnormal state of their immunologic defenses.

Dysgammaglobulinemias. As Gitlin [*1*] succinctly summarizes: "There are at least three forms of agammaglobulinemia: congenital, manifested in infancy or early childhood by repeated bacterial infections and occurring predominantly in male children; acquired, occurring in persons of either sex, the onset of infection beginning at any time from childhood to old age; and transient, occurring in a restricted period of early infancy as a consequence of inadequate gamma globulin synthesis in the first few months of life."

In the congenital form, most patients have concentrations of gamma globulin below 50 mg. per cent, almost undetectable by paper electrophoresis. Acquired agammaglobulinemia may be idiopathic or secondary to granulomatous or neoplastic disease of the lymphoid tissues. When the defect is somewhat less severe, serum gamma globulin concentrations will range up to 100 mg. per cent. There is a remarkable scarcity of plasma cells in marrow, nodes, and other tissues, to which defect the deficiency of gamma globulin is attributed. Transient agammaglobulinemia occurs in the fourth to the twelfth week of life, occasionally in the infant whose endogenous antibody production is "slow on the uptake," as the titer of passively transferred maternal antibodies falls below the minimum protective level of approximately 150 mg. per cent. Hypogammaglobulinemia occurs in the nephrotic syndrome, with concentrations of gamma globulin averaging 200 mg. per cent.

Our patients do not seem to fit into any of the agammaglobulinemic or hypoglobulinemic syndromes. Demonstration in the serum of a high normal total globulin concentration in the male infant does not support the diagnosis of agammaglobulinemia. The subsequent birth of a female sibling with the same disease entity, in whom was found a relatively normal serum electrophoretic pattern, would appear conclusively to rule out any of the forms of agammaglobulinemia as the underlying defect in her case and, by inference, in that of her brother. We considered the hypergammaglobulinemia of Janeway [*2*] as a diagnostic possibility. Clinically, the patients observed by Janeway and by others have been indistinguishable from patients with agammaglobulinemia and, like them, have frequently had secondary neutropenia, eosinophilia and lymphomonocytosis. Serum gamma globu-

lin levels have been high, ranging from 1.9 to 4.5 gm. per cent. A constant and striking discovery in Janeway's series was a diffuse plasmocytic infiltration of bone marrow and of other tissues. This finding was conspicuously absent from both of our patients, and the increase in gamma globulin was not particularly impressive in either case.

The early onset of infection in both infants is, to us, an outstanding clinical fact which weighs heavily against any of the dysgammaglobulinemias. Stubborn pyogenic skin infections began in each infant within a few days of birth and remained a problem throughout the clinical course. Cervical cellulitis developed in the male infant at two weeks of age, and pneumonia at seven weeks. Pneumonia developed in the girl at the age of eight weeks. In this age range, and particularly in the first month of life, infants are protected by immunologically adequate concentrations of maternal antibodies acquired by passive transfer. The major infections complicating congenital agammaglobulinemia do not ordinarily appear before the ninth month of life. Transient hypogammaglobulinemia may result in an earlier onset of infections, in the second month of life, but it is not ordinarily a persistent and fatal disorder, nor have multiple cases been reported in one family.

Neutropenias. No less than nine primary neutropenic syndromes are recorded. The entity bearing the closest clinical resemblance to our patients is the infantile genetic agranulocytosis of Kostmann [*3*]. His series comprised of fourteen patients from three families from the northern part of Sweden, all of whom exhibited a lethal succession of severe infections, initiated by pyoderma as early as one week postnatally. The marrow findings differed significantly from ours in that: (1) the marrow was hypoplastic, dominated by erythrocyte precursors, and (2) neutrophilic myelocytes and metamyelocytes, although diminished in numbers, were present and showed lobulation and vacuolation of their nuclei.

The Chediak-Higashi syndrome [*4,5*], described first by Beguez-Cesar [*6*], bears little resemblance to the disease affecting our patients. The absence of neutrophils with atypical granulations, and of albinism and congenital nystagmus, suffices to eliminate this bizarre entity from the differential diagnosis.

Transitory congenital neutropenia, reported recently by Stefanini [*7*] in three infants (two were siblings), born of granulocytopenic mothers, and earlier in two other siblings by Lehndorff [*8*], appears to be an immunologic neutropenia acquired by the neonate as the result of passive transfer of maternal leukoagglutinins across the placental barrier. In all five cases recorded the condition was transitory, with spontaneous recovery by the end of the first postnatal month.

The familial neutropenia of Bousser and Neyde [*9*] is a heredofamilial neutropenia, previously reported by Gansslen, to whose series they added cases of their own. The combined study reports on a total of thirteen persons from three families. The condition appears to be transmitted as a Mendelian dominant. All patients were adults and in none was the neutropenia of sufficient severity to give rise to clinical symptoms.

Fanconi [*10,11*] reported on a patient with congenital neutropenia occurring as one component of a syndrome which included pancytopenia and multiple congenital defects. His syndrome bears little resemblance to our patients.

Chronic hypoplastic neutropenia has been reported by Spaet, Dameshek [*12*] and others. There is severe chronic neutropenia with hypoplasia of granulocyte precursors and lymphomonocytosis. The condition occurs sporadically and may appear in adults as well as children. To our knowledge it has not been reported in infants; nor has more than one case occurred in a family.

Chronic benign granulocytopenia [*13–15*] has been reported in infants as young as three weeks, children, and young and middle-aged adults, usually women. The disease may terminate spontaneously after several months or persist for years. There is usually a marked granulocytopenia in peripheral blood. The marrow may be hyperplastic with a predominance of granulocyte precursors which may or may not show predominance of the immature stages. Less frequently, the marrow is reported as hypoplastic. Other than a mild anemia, attributable to episodes of infection, there is no derangement of the production of erythrocytes or platelets. Splenomegaly has not been observed and splenectomy has had no beneficial effect in the few cases in which it has been tried. Although occasional fatalities result from the intercurrent infections, most patients do surprisingly well. The disease is regarded by Adams

and Witts [*16*] as "a variant of aplastic anemia in which the main impact is on the white cells." We have found no reports of multiple cases in a family.

Cyclic neutropenia [*17*] may begin in infancy but ordinarily is non-familial and not fatal.

Primary splenic neutropenia [*18*] is non-familial and characterized by a normal or hyperplastic marrow in which immature granulocytes may predominate. The spleen is enlarged.

Some of these neutropenic syndromes are ill-defined. Neither clinically nor hematologically does there seem to be a clear dividing line between chronic hypoplastic neutropenia and chronic benign granulocytopenia. Chronic neutropenia, and even cyclic neutropenia, may accompany congenital or acquired agammaglobulinemia even in the absence of any clinical evidence of infection. Good and Varco [*19*] have suggested a common underlying defect manifesting itself in plasmocytopenia (with consequent agammaglobulinemia) combined on occasion with neutropenia or lymphopenia. Eosinophilia, monocytosis and lymphocytosis apparently may occur separately or in combination in a wide variety of agammaglobulinemic and neutropenic syndromes. Perhaps this represents a compensatory phenomenon in which any or all three cell series may participate.

The two cases under discussion appear to fall somewhere in the general category of congenital neutropenias. They likely are due to a genetic defect, although no collateral evidence is available to support this contention. The hemograms of the parents and of the five siblings who survived were normal in all respects, including granulocyte alkaline phosphatase content. No similar disease has occurred in any of the ten maternal and paternal aunts and uncles or twenty cousins of the propositi, or in the grandparents. It is possible that a granulocytopenic agent of some sort was operative in the mother during her last two pregnancies, but this seems unlikely. She herself has had no symptoms suggestive of granulocytopenia. Prolonged and close questioning produced no recollection of exposure to any of the granulocytopenia-inducing agents on Wintrobe's list [*20*].

SUMMARY

1. Two white infant siblings of opposite sex are reported on, both of whom died of congenital neutropenia.

2. The cases differ in certain respects from similar entities previously recorded.

3. We suggest that they represent a new disease, for which we propose the title, "lethal congenital neutropenia with eosinophilia."

Acknowledgment: We are indebted to Drs. Samuel R. McCreadie and Israel Diamond, pediatric pathologists of Louisville, Kentucky, who generously reviewed our case material and offered much valuable criticism and advice.

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Pathological Calcification of the Lungs Following Intravenous Administration of Calcium*

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Recently, we have observed a patient in whom extensive pulmonary calcification occurred following the intravenous administration of large amounts of calcium gluconate in an effort to control severe tetany which was unresponsive to more conservative measures. This case provides no answers to the problems involved in the pathogenesis of pathological calcification, but is presented because of its unusual features.

CASE REPORT

The patient was admitted to the Veterans Administration Hospital, St. Louis, Missouri, in November 1954, when he was twenty-nine years of age. He had been followed up since 1948 at another hospital and had been treated for numerous complications arising from regional enteritis. Medical treatment had been ineffective in controlling the severe manifestations of his disease, and surgery had been performed at three different times for the excision of involved segments of the small bowel and revision of the gastrointestinal tract. During the last of these procedures a jejunotransverse colostomy had been performed, and the total small bowel length distal to the ligament of Treitz had been decreased to twenty-four inches. His clinical course following this procedure had been characterized by manifestations of intestinal malabsorption including macrocytic anemia, mild hypoalbuminemia, and failure to gain weight. Diarrhea had been persistent, and intermittent febrile episodes with severe cramping abdominal pain, nausea and vomiting had been frequent.

During the next three years he continued to have recurrent symptoms attributed to acute and chronic enterocolitis, although several roentgenographic studies of the gastrointestinal tract failed to demonstrate specific abnormalities of the remaining segments of the small bowel and transverse colon. On gastroscopic examination the gastric mucosa was found to be atrophic; gastric analysis yielded diminished amounts of free hydrochloric acid.

On November 19, 1957, the patient was readmitted to the hospital with the same complaints as previously noted. He was a chronically ill, malnourished white man weighing 102 pounds. The blood pressure was 110/70 mm. Hg; pulse and respiratory rates were 100 and 16 per minute respectively. The tongue and mucous membranes appeared normal except for marked pallor. Examination of the heart, lungs and nervous system revealed no abnormalities. The abdomen was scaphoid, with multiple well healed surgical scars in the left lower quadrant. There was no clubbing or edema. A roentgenogram of the chest was within normal limits. (Fig. 1.)

He remained extremely weak and intermittently febrile with uncontrolled diarrhea and frequent cramping lower abdominal pain. On January 1, 1958, after he first complained of perioral numbness and muscular twitching, he was found to have a Chvostek's sign. Treatment with orally administered calcium lactate,† 2.4 gm. daily, gave temporary improvement. Shortly thereafter, however, pain and tenderness developed in the left calf and thigh with twitching of the left hand. On January 10, 1958, therapy was started with 500,000 units of activated ergosterol administered intramuscularly twice weekly. Ten days later spasm of the facial muscles, protrusion of the tongue, carpopedal spasm, and periods of prolonged inspiratory apnea developed, which were relieved by the administration of large amounts of calcium gluconate. During a period of approximately fifteen hours he was given a total of 47 gm. of calcium gluconate‡ by intravenous infusion in 5 per cent dextrose in water before sustained improvement was noted. Frequent electrocardiograms showed only sinus tachycardia and slight S-T segment depression. Unfortunately, the serum calcium concentration

† Calcium content 13 per cent.

‡ Given as Calcium gluconate-glucoheptonate (Abbott) with a calcium content of 9 per cent.

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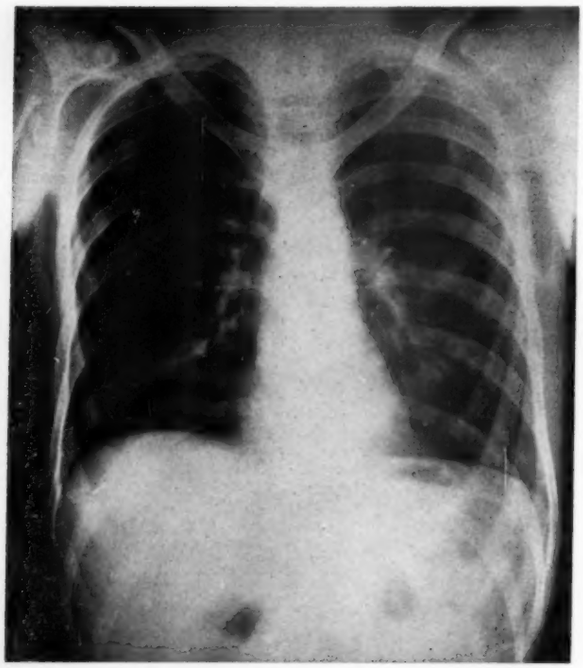


FIG. 1. Roentgenogram of the chest taken on November 20, 1957, prior to the intravenous administration of calcium.

during this period is not known. Twenty-four hours after the completion of the calcium infusion the serum calcium was 14.4 mg. per 100 ml., serum phosphorus 5.6 mg. per 100 ml., carbon dioxide combining power 14.3 mEq. per L., serum sodium 139 mEq. per L., and blood urea nitrogen 11 mg. per 100 ml.

On February 16, 1958, the patient complained of a sensation of swelling of his tongue. A facial spasm developed again with drawing down of the corners of the mouth. The serum calcium concentration was 7 mg. per 100 ml.; serum phosphorus 3.3 mg. per 100 ml. Because of the large amounts of calcium previously required, he was given 20 gm. of calcium gluconate in 1,000 ml. of 5 per cent dextrose in water during a period of approximately eight hours; the daily oral administration of 20 gm. of calcium gluconate was started. Between March 3 and April 1 eight separate infusions were administered each containing 10 gm. of calcium gluconate; in addition, he was given two separate infusions containing 40 gm. and 20 gm. respectively, and one infusion of 50 gm. in an effort to control manifestations of tetany. In spite of these measures his serum calcium concentration on March 4 was 6.6 mg. per 100 ml. and the serum phosphorus concentration was 3.5 mg. per 100 ml. On March 25, the following values, mg. per 100 ml., were obtained: serum calcium 7.6, serum phosphorus 3, blood urea nitrogen 10.5.

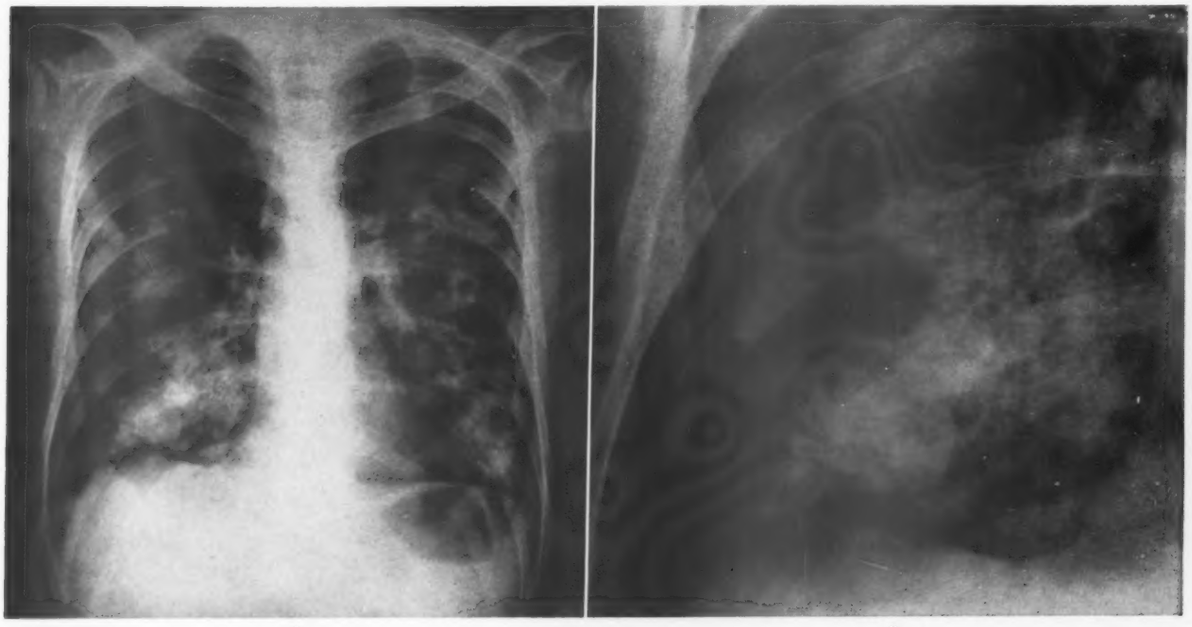
During this period of intensive intravenous administration of calcium he showed clinical evidence of hypercalcemia manifested by somnolence, nausea and vomiting on only one occasion. At this time the serum calcium concentration was 20.3 mg. per 100 ml. and the serum phosphorus was 3.3 mg. per 100 ml. The following day the serum calcium concentration had fallen to 14.3 mg. per 100 ml. No further calcium was given intravenously, but he received 100 gm. of calcium gluconate and 500,000 units of dihydrotachysterol orally each day. The serum calcium concentration was normal on April 29, and he was discharged from the hospital markedly improved.

By July 8 he had gained nineteen pounds; the serum calcium concentration was normal, and the daily oral administration of calcium gluconate was reduced to 50 gm.

His next hospital admission was on August 22, 1958, because of pains in the calf and thigh muscles, increasing weakness, and episodes of nausea and vomiting. His general appearance had not changed. There was no cyanosis or clubbing. The serum calcium concentration was 9.9 mg. per 100 ml.; serum phosphorus 4 mg. per 100 ml.; blood urea nitrogen 9 mg. per 100 ml.; serum albumin 4.2 gm. per 100 ml., and serum globulin 3.1 gm. per 100 ml. On roentgenographic examination of the chest a patchy, dense infiltration compatible with pulmonary calcification was seen diffusely scattered throughout both lungs. (Figs. 2 and 3.) He denied any increase in dyspnea; there had been no cough or chest pain, or intercurrent infections of the respiratory tract. Results of intermediate strength P.P.D. and histoplasmin skin tests were negative. Pulmonary function studies revealed only an increase in residual lung volume compatible with mild emphysema. Calcium balance studies were attempted but could not be carried to completion. At this time his oral intake of vitamin D was 100,000 units daily. The serum calcium and phosphorus concentrations remained normal. The long bones and pelvis appeared normal on roentgenographic examination. The serum alkaline phosphatase was 4.8 Bodansky units per 100 ml. Slit lamp examination of the cornea was performed and no calcium deposits were observed.

On December 20, 1958, fever with a non-productive cough developed; and cultures of the sputum yielded a growth of Candida albicans and a mixed growth of pneumococci, non-hemolytic streptococci and Staphylococcus aureus. Therapy with tetracycline and later chloramphenicol was started, but no initial response was noted. On January 6, 1959, therapy with ACTH, 20 units administered intramuscularly twice daily, was instituted and he slowly improved to the extent that discharge from the hospital was possible.

On April 7, 1959, he was readmitted in an extremely weakened condition. Diarrhea and abdominal pain had increased; anorexia, nausea and vomiting had contributed to the development of severe dehydration and prostration. The blood pressure was 70/0 mm. Hg, the pulse rate was 130



2 3

FIG. 2. Roentgenogram taken on August 22, 1958, demonstrating the extensive pulmonary calcification observed at the time of readmission to the hospital following the administration of calcium during his previous hospital admission.

FIG. 3. Enlargement of Figure 2 which demonstrates the appearance of the base of the right lung.

per minute, and the temperature was 98.6°F. Examination of the heart and lungs revealed no abnormalities. There was no cyanosis or clubbing. The leukocyte count was 42,750 per cu. mm.; hemoglobin 12.5 gm. per 100 ml.; blood urea nitrogen 13.5 mg. per 100 ml.; serum sodium 135 mEq. per L.; serum potassium 3.1 mEq. per L.; serum carbon dioxide combining power 9.8 mEq. per L.; serum chloride 108 mEq. per L.; serum calcium 8.6 mg. per 100 ml.; serum phosphorus 3.4 mg. per 100 ml. The specific gravity of the urine was 1.020, protein and sugar were absent, there were 3 to 4 white blood cells per high power field. A shift of the electrical axis towards the right and the appearance of clockwise rotation were noted on the electrocardiogram. Vectorcardiogram was interpreted as compatible with cor pulmonale. Tetracycline and chloramphenicol were administered and measures were instituted to correct his severe dehydration and acidosis. He did not improve, and died quietly on April 10, 1959.

The findings at autopsy were as follows: the lungs were heavy and firm. The right lung weighed 600 gm., the left 500 gm. The pleural surfaces were gray and glistening with no adhesions. Over the surface of the lungs and throughout the parenchyma there were hard confluent areas of a granular gray substance which cut with difficulty and had the consistency of pumice stone. (Fig. 4.) In the right lower lobe there was an abscess measuring 7 cm. in diameter filled with brownish necrotic material and lined by fine gritty calcifications. The smaller bronchi in the left lung contained whitish yellow plugs of tenacious material. The pulmonary vessels were normal; there was no evidence of thrombosis or embolism. Microscopically there were numerous foci of calcification which ranged in size from very small to the diameter of an alveolus. Most of the deposits lay within the walls of alveoli; the alveolar septums were moderately thickened and often fibrotic. (Fig. 5.) In larger focal areas which sometimes appeared to correspond to secondary lobules of the lung parenchyma, there was total replacement of the normal architecture by fibrous tissue. The calcific deposits lay randomly distributed throughout the fibrous tissue in approximately the same amounts as in the areas having relatively normal parenchyma. (Fig. 6.) The bronchi appeared normal except for occasional deposits of calcium beneath the bronchial epithelium. In all areas of the lung the deposits took the von Kóssa and alizarin stains. The heart weighed 300 gm. and appeared normal except for small thrombotic masses which were attached to the endocardial surface of the left atrium, and a large grayish white thrombus which was attached to the endocardial surface of the left ventricle. The endocardium between the thrombotic masses was normal. The liver weighed 1,500 gm. and was pale yellow in color; microscopically the liver parenchyma was extensively replaced by fat. The remaining small intestine was soft and friable and had a smooth mucosal surface with a normal rugal pattern. The total small bowel length was 107 cm. The parathyroid glands could not be identified. The stomach and kidneys appeared normal on gross inspection. Otherwise, the autopsy revealed no abnormalities.

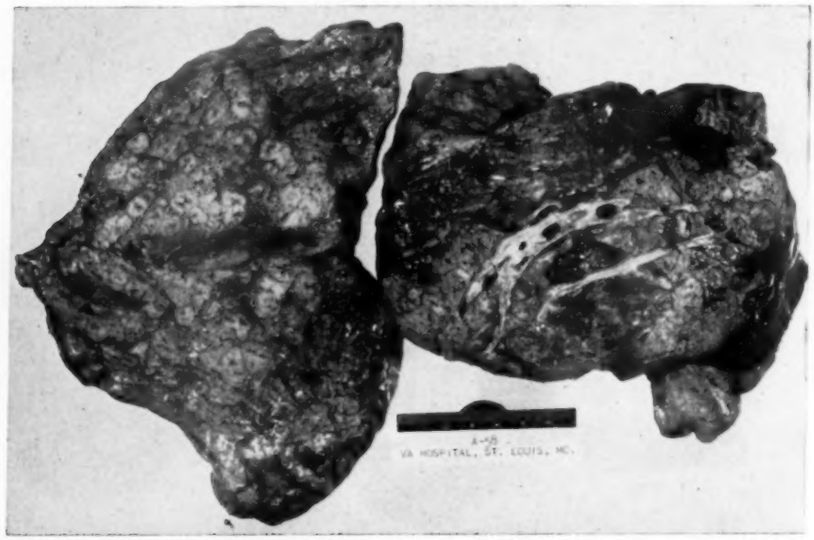
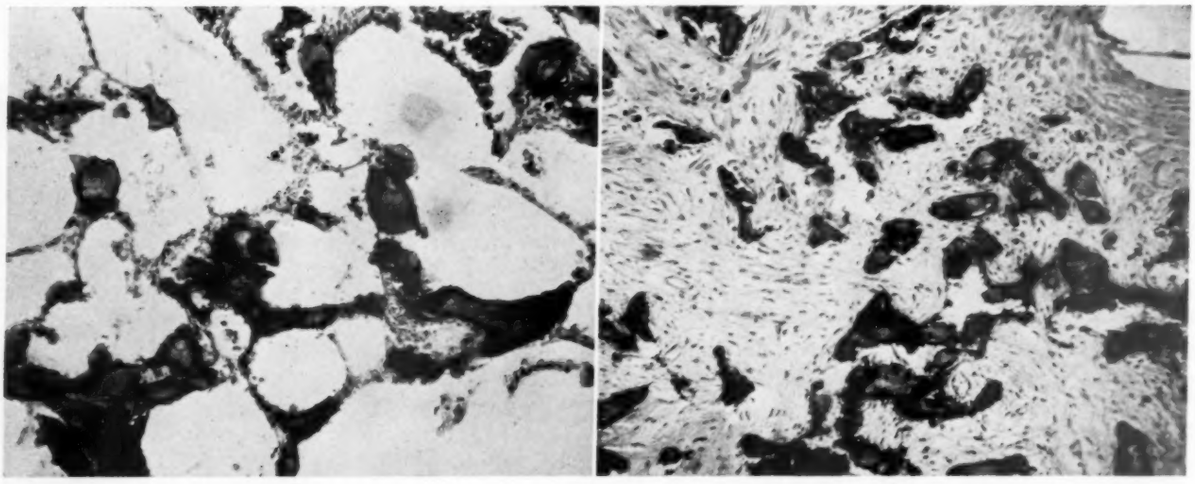


FIG. 4. Cut surface of the left lung showing the extensiveness of the calcification.



5 6

FIG. 5. Microsection of the lung showing slightly thickened and fibrotic alveolar septums which contained numerous deposits of calcium.

FIG. 6. Microsection of the lung obtained from an area of extensive fibrosis. Deposits of calcium were scattered throughout these areas in a random distribution.

COMMENTS

Pathological or "metastatic" calcification of the lungs is known to occur in a wide variety of disease processes. Mulligan [*1*], in a review of metastatic calcification in 1947, noted the occurrence of calcification of the lungs in sixty-six of a total of ninety cases gathered from the literature up to that time. Thirty-five of these ninety patients were found to have neoplastic or other destructive lesions of bone which included metastatic carcinoma, multiple myeloma, osteomyelitis, myelogenous leukemia, metastatic sarcoma, primary sarcoma of bone, metastatic melanoma, tuberculosis of bone, osteopetrosis and osteitis deformans. In sixty per cent of these thirty-five patients with bone disease calcification involving the lungs was observed. Metastatic calcification with pulmonary involvement was also observed in association with chronic renal disease, hyperparathyroidism due to adenomas and hypervitaminosis D. Bauer and Freyberg [*2*] reported a case of pathological calcification with pulmonary involvement thought to be secondary to vitamin D intoxication. Pulmonary calcification in the form of small nodules or linear streaks which outlined the alveolar septums was re-

ported in a patient with metastatic calcification associated with excessive intake of milk and alkali [*3*]. None of these patients had pulmonary calcification without the involvement of other organs.

A morphologically distinct form of diffuse pulmonary calcification, pulmonary alveolar microlithiasis, was recently reviewed by Sosman et al. [*4*]; in some aspects this case resembles those described in that category. However, the development of pulmonary calcification concomitantly with the administration of large amounts of soluble calcium salts and the difference in microscopic appearance distinguishes this case from pulmonary alveolar microlithiasis.

During the eight months prior to the detection of diffuse pulmonary calcification this patient was given calcium supplementation orally in the form of calcium lactate and calcium gluconate, and in addition was given between 250 gm. and 275 gm. of calcium gluconate intravenously in divided amounts ranging from 10 to 50 gm. given in six to eight hour infusions during a span of two months. These amounts of calcium are far in excess of those usually required in therapy and were given only when it became apparent that more conservative amounts were not producing a sustained response.

Hypocalcemic tetany, although reported to occur following extensive small bowel resection [*5,6*], is not a common finding. Balance studies in these patients have demonstrated that although the reabsorption of calcium from the intestine may be impaired because of the decrease in length of the small bowel, the absorption of dietary calcium occurs normally from the remaining upper small intestine as long as the pH of the intraluminal fluid is sufficiently low [*6,7*]. Atrophic gastric mucosa and decreased gastric acidity were demonstrated in this patient several years prior to the development of tetany, and may have contributed significantly to the occurrence of hypocalcemia by decreasing the absorption of calcium from the remaining upper small intestine. Other deficiencies may also have played a significant role in the development of tetany; the extreme refractoriness of the patient's tetany to treatment with calcium gluconate suggests that this was true. Recently, much attention has been given to the role of hypomagnesemia in the production of central nervous system disturbances, including convulsoid states which closely resemble hypocalcemic tetany [*8–11*]. Whether or not this patient, in fact, had a magnesium deficiency to account for his slow response to intravenous calcium gluconate cannot be answered.

Although hypercalcemia is regarded as the basis for the development of pathological calcification of the lungs and other organs in many disease processes, serum phosphate levels have also been considered to be important in this process, and pathological calcification has been observed in conditions in which high serum phosphate concentrations were present with only slightly increased or normal serum calcium levels [*12*]. In this patient the serum phosphate levels were never elevated.

Vitamin D when given in large doses, as noted previously, may lead to extensive pathological calcification; the patient herein described was receiving 500,000 units of activated ergosterol intramuscularly twice weekly together with 500,000 units of dihydrotachysterol orally daily during the period of intensive administration of intravenous calcium. Whether or not these sterols contributed significantly to the observed calcification is difficult to ascertain, but seems likely. Vitamin D has been observed to delay the clearance of intravenously administered calcium chloride from blood when given to animals prior to calcium infusion [*13*]; in this manner it may have contributed to the development of the observed pulmonary calcification.

Extensive pathological calcification has been reported to occur in animals following the parenteral administration of soluble calcium salts, and pulmonary calcification which closely resembled the calcification seen in this patient has been observed [*14*]. To our knowledge, no such observation has previously been reported in human beings.

It is also pertinent to consider briefly the possible role of nutritional deficiencies in the development of soft tissue calcification. Highman and Daft [*15*] described the occurrence of calcification in various organ systems, including the lungs, in mice which were fed a purified low protein, choline-deficient diet. The hepatic changes in our patient were identical with those produced in experimental animals by diets deficient in choline, and it is reasonable to assume that numerous nutritional deficiencies existed after such a long period of intestinal malabsorption.

Whether or not the marked decrease in the area of the small bowel surface contributed significantly to the development of pathological

calcification by partially blocking or delaying the excretion of calcium via the intestine should perhaps be considered. Howard [*16*] is of the opinion that there is no positive excretory mechanism for the elimination of excess calcium by the gastrointestinal tract, and Baylor et al. [*17*] were unable to demonstrate any significant change in excretion of fecal calcium following administration of intravenous calcium. McCance and Widdowson [*18*] were unable to produce an increase in excretion of calcium by the gastrointestinal tract by the intravenous infusion of calcium and concluded that the intestinal excretion of calcium does not vary with changes in plasma levels. Thus, it would seem that intestinal excretion does not play a significant role in lowering elevated serum calcium levels and that the decreased small bowel surface area was not important in this regard.

Up to this point the features which may have influenced the occurrence of pathological calcification in this patient have been discussed without considering the question of why this phenomenon was observed only in the lungs. The release of carbon dioxide from the alveolar surface resulting in a zone of relative tissue alkalinity may, in part, explain why there should be no surprise to find the lungs so extensively involved in this process. However, the question of why other organs such as the kidneys, stomach and eyes were not equally involved remains unanswered. The lungs were the first major site of significant pH alteration through which high concentrations of calcium gluconate passed following infusion via the peripheral veins. However, the fact that abnormally high serum calcium levels were observed as long as twenty-four hours after the intravenous infusions makes it seem unlikely that the location of the lungs was of major importance in determining the site of deposition of the calcium.

SUMMARY

A case is reported of extensive pulmonary calcification which occurred following the administration of large amounts of calcium gluconate, vitamin D and dihydrotachysterol in an effort to control severe manifestations of tetany. Whether or not the extreme refractoriness of the patient's symptoms to the administration of calcium was due to other factors (i.e., hypomagnesemia) is not known.

Pathological calcification of the lungs occurred to a degree disproportionate to any which may have escaped detection in other organs. There is no evidence that the lungs were altered in any way by factors which would account for this specific localization.

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Metabolic Observations in Adult Hypophosphatasia*

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HYPOPHOSPHATASIA, established as a disease entity and named by Rathbun [*1*] in 1948, is now recognized as an inborn error of metabolism [*2*], possibly inherited through the action of an autosomal recessive gene. The disorder is characterized by a varying degree of abnormal mineralization of the bone, lowered serum and tissue alkaline phosphatase activity, and an increased urinary excretion of "phosphorylethanolamine." The reported cases of hypophosphatasia were reviewed in 1957 by Fraser [*2*], who divided the disease into four classes according to the age of onset and severity of the clinical and radiologic manifestations.

This paper reports the results of metabolic balance studies of calcium, phosphorus and nitrogen in a patient with the adult form of hypophosphatasia, the observations being made in control periods and during the administration of corticoids and estrogen. An improved method for the quantitative measurement of urinary phosphorylethanolamine is also described.

METHODS

Two prolonged metabolic balance studies were conducted in the Metabolic Ward of Walter Reed Army Hospital using the procedures employed in this department, as previously described [*3*]. Solid diets, identical from day to day, were used during each study. Urine collection periods were forty-eight hours in duration throughout the first study, and ninety-six hours in duration throughout the second study, with the exception of the period after control when collections of forty-eight hours' duration were employed. Completeness of the urine collections was checked by determinations of urine creatinine. Stool collection periods were six days in duration and were apportioned by alternating carmine and charcoal markers. The balance data are charted according to Reifenstein, Albright and Wells [*4*]. An equilibrium period of six days (not shown in the figures) was obtained before each study.

The diet was adequate in calories (37 calories per kg.) and in protein (1.5 gm. per kg.). The dietary phosphorus was 1.2 gm. per day and calcium was 1.0 gm. per day (administered in part as 7.5 gm. of calcium gluconate per day). After eighteen days of control collections, administration of Meticorten® (prednisone) was begun in a dosage of 5 mg. three times daily for twelve days. The dosage was then increased to 10 mg. three times daily for twelve days and finally to 20 mg. three times daily for twelve days. The administration of steroid was then discontinued abruptly and twelve days of collections were obtained after steroid therapy.

The equilibrium period of the second study began forty-two days after completion of the first study. The diet contained 39 calories per kg., 1.8 gm. protein per kg., 1.3 gm. of phosphorus, and 1.1 gm. of calcium (which included the oral administration of 6.0 gm. of calcium gluconate daily). After eight days of control collections, administration of stilbestrol was begun in a dosage of 15 mg. daily for twelve days followed by six days during which no medication was given.

Roentgenograms and clinical laboratory studies were obtained at regular intervals throughout both balance periods (see Case Report). Serum alkaline phosphatase activity was determined in the laboratory of the Department of Metabolism by the method of Shinowara, Jones and Reinhart [*5*]; frequent duplicate aliquots were also analyzed by the same method in the clinical laboratory of Walter Reed Army Hospital. Calcium, phosphorus, nitrogen and creatinine analyses were performed by standard methods [*6*].

Urinary phosphorylethanolamine was measured by one of us (H. R.). A two-day sample of the patient's urine was evaporated to a volume of 200 ml., 2.5 cc. of the residue (corresponding to 63 ml. of the original urine) was used for analysis, employing the procedure to be described.

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O-phosphoryl ethanolamine was prepared as a standard by the method of Ferrari and Ferrari [7]. Its rate of travel on a 100 cm. Dowex-50 column was found to be equivalent to that of taurine, using the pH 3.4 buffer of Moore and Stein [8] with the column held at 38°c. Both of these compounds are markedly acidic and travel practically with the solvent front. One milliliter eluent fractions were collected; 0.5 ml. were analyzed with ninhydrin in order to find the tubes containing the compound. The remaining 0.5 ml. of the proper tubes were combined and hydrolyzed in a sealed tube at 105 degrees for sixteen hours at pH 4 according to the method of Cherbuliez and Bouvier [9]. O-phosphoryl ethanolamine is unusual in that it is hydrolyzed most rapidly under mild conditions. The hydrolysate was evaporated *in vacuo* and then rechromatographed. One hundred milliliters of the pH 3.4 buffer was run through the column and the eluent discarded; 50 ml. of pH 6.7 buffer [8] was run through next, the eluent again being discarded. This was followed by a buffer of pH 11.0 [8]. A ninhydrin-reactive fraction emerged from the patient's urine; its rate of travel on the column corresponded to that of pure ethanolamine, and was measured by the photometric ninhydrin method of Rosen [10]. This method is quite specific, since only a compound which meets the following requirements could be measured as phosphoryl-ethanolamine: it must be (1) an acidic compound, and (2) an acidic compound which will hydrolyze rapidly near neutral pH, to yield a basic ninhydrin reactive compound that is chromatographically indistinguishable from ethanolamine.

CASE REPORT

While stationed at an overseas base in June 1956, a thirty-six year old Air Force sergeant slipped and struck his right knee on a concrete floor. There was immediate severe pain in the knee which forced him to use crutches for ambulation during the ensuing week. Pain persisted, and during a period of travel in September 1956, roentgenograms of the right knee, obtained at two different hospitals, revealed no abnormalities. However, because of continued pain and a limping gait, additional roentgenograms were obtained at the patient's home base. These roentgenograms included the entire right femur and demonstrated an incomplete fracture of the femoral shaft. (Fig. 1.) The patient was placed at bed rest in a long leg cast for seven weeks and then permitted a walking cast and crutches. However, pain occurred with any movement of the leg. The patient was returned to the United States in January 1957 for further therapy.

A biopsy was performed at the site of the persistent fracture on March 18. At surgery the femoral cortex was noted to be vascular and thin. A window was cut in the cortex and the marrow cavity was curetted. Cultures of fluid from the marrow cavity were negative for bacteria, tubercle bacilli and fungi. The pathologic condition of the bone, interpreted by Dr. Lent Johnson of the Armed Forces Institute of Pathology, showed fibrosis and osteoporosis secondary to fracture, with small delicate trabeculae which failed to mature, calcify or reconstruct. Because of continued failure of the fracture to heal, the patient was transferred to this hospital in October, 1957.

Past history revealed that at nineteen years of age the patient fractured his left humerus in an automobile accident; the arm was placed in a plaster cast and the fracture healed within six weeks. Malaria and jaundice developed at the age of twenty-two. He underwent an appendectomy at the age of twenty-six. All his teeth were extracted prior to the age of thirty, apparently because of severe caries; the patient could not recall when he lost his deciduous teeth. An episode of hematemesis at the age of thirty-three was investigated by three upper gastrointestinal series. These failed to reveal the source of the bleeding, and the patient had no other subsequent history suggestive of peptic ulceration. No history could be elicited of delayed growth or maturation or of rickets during childhood.

The patient was married but had no children. His parents and two siblings were alive and well. Careful questioning failed to reveal any history of bone disease or developmental defect in any blood relative. Determinations of serum alkaline phosphatase at another hospital showed the patient's mother to have a level of 1.0 Bodansky units (normal range 1 to 3 units), the father 1.1 Bodansky units, and a brother 1.1 Bodansky units.

On admission to Walter Reed Army Hospital the patient was a well developed, well nourished, adult white man who appeared to be in good general health. He walked with a limp, favoring his right leg, and used a cane for support. Complete edentia was noted along with a well healed appendectomy scar, but otherwise the physical examination revealed no abnormalities.

The laboratory studies showed the white blood cells to be consistently normal in number and morphology except for a consistent lack of leukocyte alkaline phosphatase activity [11]. The hemoglobin, hematocrit and erythrocyte sedimentation rate were normal. Results of the serological tests for syphilis were negative. The urinalysis was within normal limits. Serum calcium determinations made repeatedly during a ten-month period averaged 5.1 mEq., and repeated serum phosphorus determinations in the same period averaged 4.3 mg. per cent. Serum alkaline phosphatase levels were consistently below 2 S.J.R. units (see Results); the serum acid phosphatase was normal. The serum sodium was 147 mEq./L., chloride 105 mEq./L., and potassium 4.5 mEq./L. The serum proteins were 7.0 gm. per cent with an electrophoretic pattern of 54.2 per cent albumin and 6.3 per cent alpha-1, 9.7 per cent alpha-2, 11.6 per cent beta- and 16.2 per cent gamma globulin. The blood urea nitrogen and

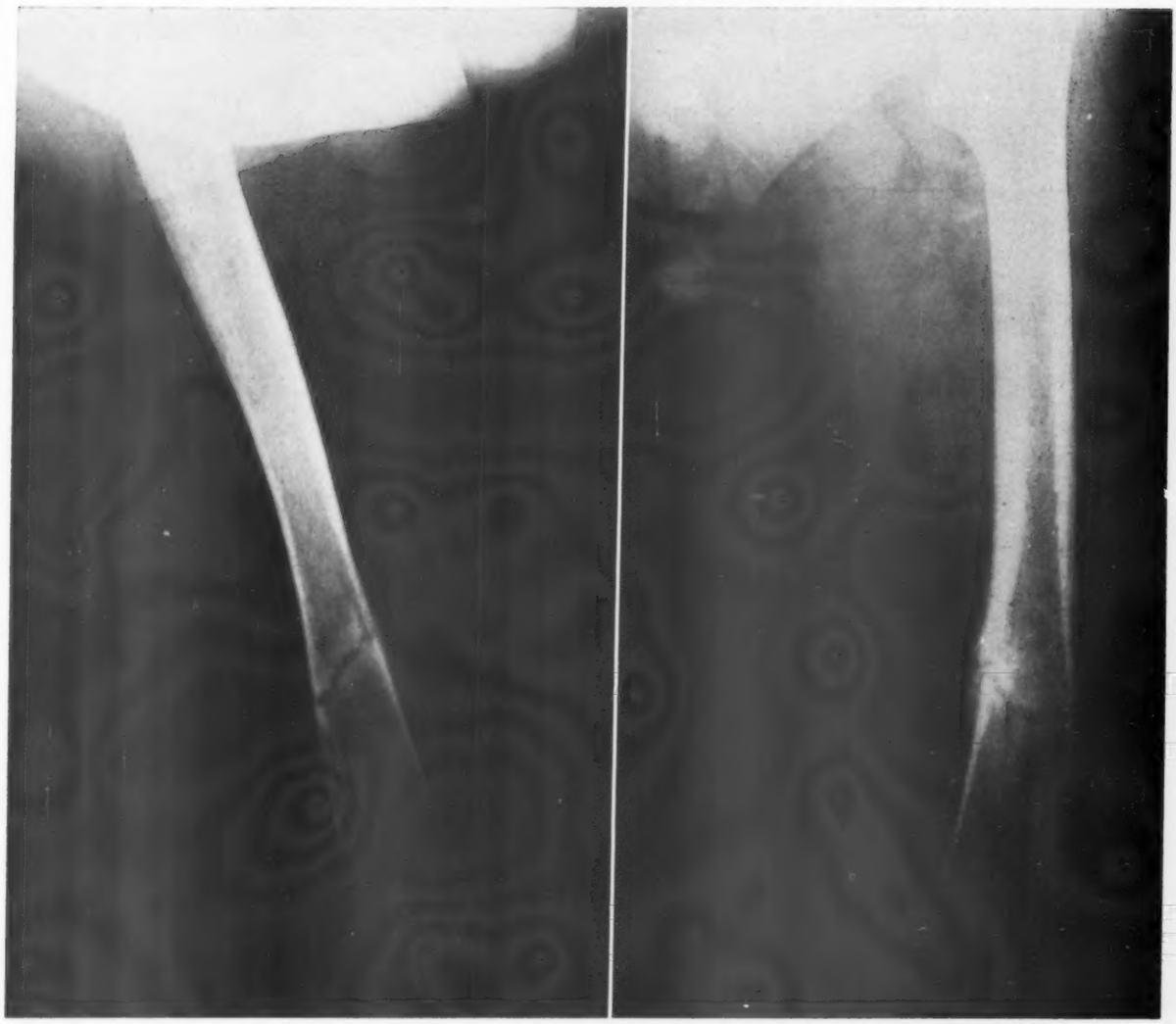


FIG. 1. Anteroposterior and lateral views of the right femur. These roentgenograms were taken nine months after injury and show the incomplete fracture with some callous formation.

creatinine levels were normal, as was phenosulfonphthalein excretion. The renal clearance of phosphorus was 8.6 cc./ minute, the renal tubular reabsorption of phosphorus was 92.9 per cent of the filtered phosphorus load. The patient retained 55.2 per cent of an intravenous injection of calcium given as 100 mg./kg. of calcium gluconate in 300 cc. normal saline solution over a three-hour period. The basal metabolic rate was minus 8, serum protein bound iodine 6.0 μg. per cent, there was a thyroidal uptake of 17 per cent of a tracer dose of radioiodine. A glucose tolerance test showed 77 mg. per cent when fasting, 124 mg. per cent at a half hour, 82 mg. per cent at one hour, 77 mg. per cent at two hours, and 76 mg. per cent at three hours. The patient excreted 4.9 gm. of xylose in the urine within five hours after the oral administration of 25 gm. The urinary 17-hydroxycorticosterone excretion was 6.8 mg., the 17-ketosteroid excretion was 14.6 mg. in twenty-four hours. The urinary excretion of phosphorylethanolamine was high; using the method described, 30 mg. per day was excreted.

After the diagnosis of hypophosphatasia was established by laboratory procedures, additional special studies were obtained, as will be recorded. The patient remained ambulatory throughout his hospital stay.

During an epidemic of Asian influenza the patient had an acute febrile illness characterized by malaise, anorexia, cough, arthralgia, an inflamed pharynx, and a liver which was enlarged and palpable. All symptoms and findings subsided spontaneously after several days, the white blood cell count remained normal, and throat cultures were negative. At the time of the transient hepatomegaly the serum alkaline phosphatase was recorded at 2.8 S.J.R. units, the only value within the normal range of 2 to 8 S.J.R. units during hospitalization.

After initial baseline procedures, metabolic balance

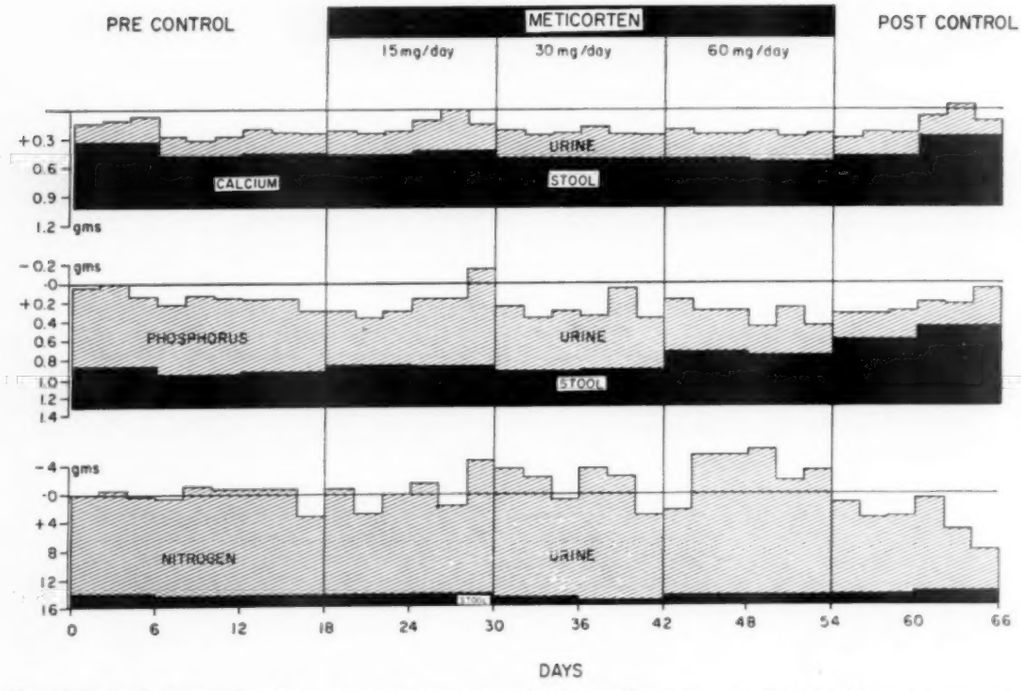


FIG. 2. Data from the first balance study are charted after Reifenstein et al. [4]. Equilibration period not shown.

studies were completed as described (see Results). A transient episode of nervousness and anxiety developed with the abrupt withdrawal of prednisone therapy. Throughout hospitalization and several convalescent leaves, the patient's pain gradually subsided and his gait became normal. After ten months at this hospital (twenty-eight months after the original fracture) there was sufficient roentgenographic evidence of bone healing and freedom of leg pain to permit return of the patient to his military duties.

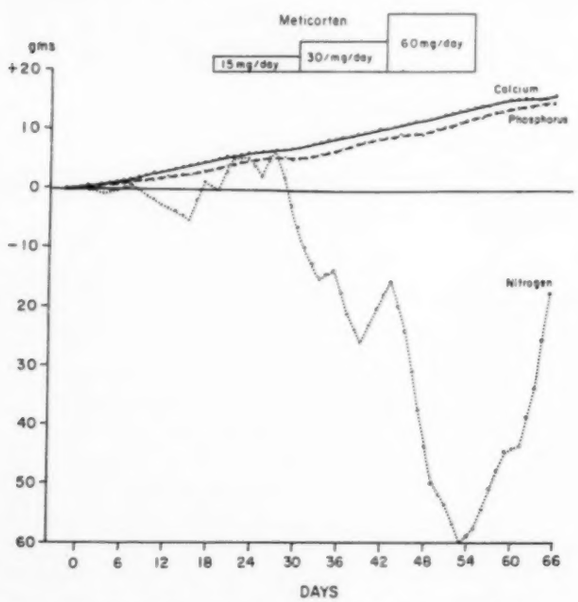


FIG. 3. Cumulative balances from the first study show a marked dissociation of nitrogen from calcium and phosphorus in response to varying doses of Meticorten.

RESULTS

First Balance Study. Throughout the entire first balance study the patient remained in consistently positive calcium and phosphorus balance. (Fig. 2.) The rate of retention of bone minerals, as shown by cumulative balance, (Fig. 3) did not appear to be influenced by prednisone therapy in any of the three doses employed. The administration of prednisone did not cause any appreciable or significant change in fecal or urinary calcium. The urinary phosphorus was not increased by the administration of prednisone except for a single two-day collection period occurring after ten days on a dosage of 15 mg. per day. An increase in stool phosphorus during the last twenty-four days of balance accompanied the administration of aluminum hydroxide. This was compensated for by a decrease in urinary phosphorus.

The patient was in approximate nitrogen equilibrium during the control period. When the higher doses were administered during

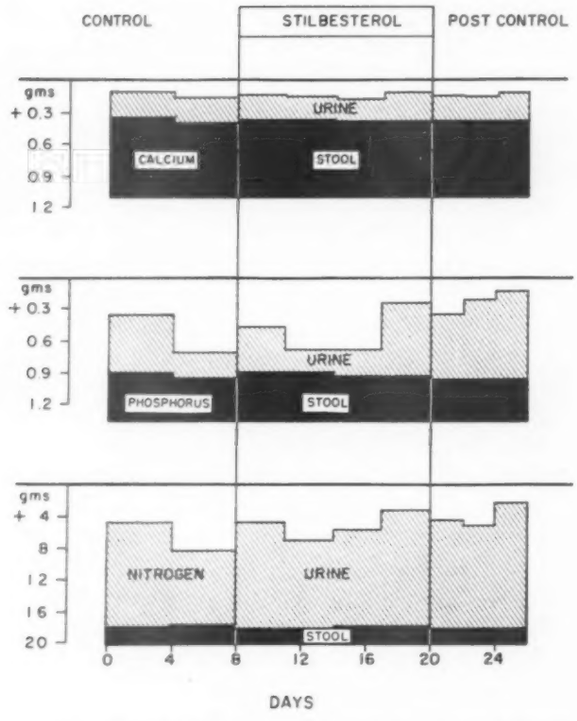


FIG. 4. Data from the second balance study are charted after Reifenstein et al. [*4*]. Equilibration period not shown.

prednisone therapy the nitrogen balance became markedly negative. This resulted in a cumulative loss of 60 gm. of nitrogen, and a clinical weight loss of nine pounds. In the period after control the nitrogen balance became markedly positive, restoring much of the previous weight loss. Nitrogen retention or loss appeared to be entirely independent of calcium or phosphorus. The theoretical phosphorus balance based on a N:P ratio of 14.7 and a Ca:P ratio of 2.23 [*4*] would indicate that 2.6 gm. of phosphorus should have been retained by the last day of prednisone administration, whereas the measured cumulative phosphorus showed a gain of 11.7 gm., 9.1 gm. greater than the theoretical value.

Second Balance Study. Throughout this study the patient was in persistently positive calcium, phosphorus and nitrogen balance. (Fig. 4.) Because of the higher protein diet and the fact that catabolic hormones were not being administered, nitrogen was retained throughout the study, and this may explain in part the greater daily retention of phosphorus (Fig. 5) than in the first study. The theoretical retention of phosphorus [*4*] at the end of the study was 9.6 gm. compared to a measured retention of 11.9 gm.

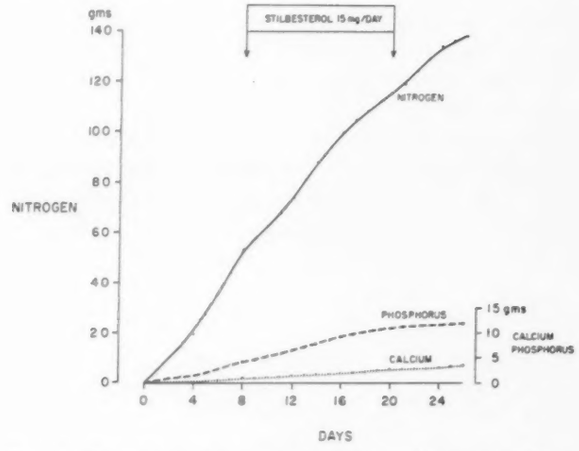


FIG. 5. Data from the second study recharted to show cumulative balances of nitrogen, calcium and phosphorus.

Administration of stilbestrol resulted in no striking change in balances when compared to the control period, and no significant difference in the rate of retention of calcium, phosphorus or nitrogen was evident. However, in the period after control phosphorus retention was lessened.

Serum Alkaline Phosphatase Activity. Abnormally low values for serum alkaline phosphatase activity were consistently found throughout both balance studies. Determinations of twenty-two samples performed in duplicate in our laboratory showed a mean level of 0.9 S.J.R. units, with a range of 0.5 to 2 units. No difference in serum alkaline phosphatase activity could be detected during prednisone therapy at any of the three doses employed or with the administration of stilbestrol. A series of nineteen serum samples sent for routine analysis to the clinical laboratory of this hospital at intervals throughout the entire length of hospitalization showed a mean value of 1 S.J.R. units.

COMMENTS

Of the four instances of adult hypophosphatasia listed by Fraser [*2*], only the patient described by Macey has been reported on in detail [*12*]. This white man had "rickets" with genu valgum as a child, and bilateral pseudofractures in the middle third of both femurs developed at the age of thirty-five. The findings in a thirty year old white woman with hypophosphatasia who survived multiple bony deformities in childhood and dwarfing to reach adult life have been presented in abstract form by Owen and Peskin [*13*]. Their patient also suffered a femoral fracture as an adult. Other adults who show

typical biochemical findings of hypophosphatasia but lack skeletal abnormalities have been reported on in family surveys of children with the disease.

Our patient appears to represent the sixth [*2,12,13*] case of adult hypophosphatasia to be reported and the first in which detailed metabolic balance data have been obtained. In this patient it is difficult to determine if the delay in bone healing was solely the result of the disease, as the slowness of repair may have been influenced in part by the initial failure in detection of the incomplete fracture. A previous humoral fracture healed promptly, but in that instance adequate splinting had been instituted without delay and the fracture did not involve a weight-bearing bone. However, the appearance of thin delicate bone trabeculae with poor maturation on the biopsy specimen of the bone and the occurrence of a fracture of the shaft of the femur with only minimal trauma, would suggest that a metabolic defect was present. The early loss of all permanent teeth in this patient bears certain similarity to the premature loss of deciduous teeth in patients in whom hypophosphatasia is diagnosed in childhood. However, no historical evidence suggesting childhood manifestations of this disease could be uncovered in this patient.

The progressive retention of bone minerals in two prolonged balance periods is compatible with the observed gradual healing of the femoral fracture. Prednisone was administered to this patient in the hope of reproducing the beneficial results reported by Fraser and Laidlaw [*14*], and to give further information on the response of hypophosphatasia to various doses of adrenal steroids. During the administration of prednisone, nitrogen was lost from the body in amounts proportional to the increasing doses employed. The hoped for increase in retention of bone minerals did not occur with prednisone therapy; instead, calcium and phosphorus continued to be retained at rates equivalent to those during control and after control balance periods. Thus a dissociation of nitrogen balance from that of phosphorus balance occurred, phosphorus retention progressed at a steady rate while nitrogen balance varied from initial equilibrium to periods of loss at three different rates, and finally to marked retention. The tendency of steroids to increase fecal calcium in sarcoidosis [*15*] was not duplicated in this single study in hypophosphatasia.

The majority of data in balance studies on human beings, with respect to the effect of estrogens on calcium, phosphorus and nitrogen metabolism, have been reported in patients with osteoporosis of varying etiology. It has been shown that the administration of estrogen will stimulate endosteal bone formation in pigeons and mice [*16*], and decrease fecal and urinary excretions of calcium and phosphorus in balance studies in postmenopausal osteoporosis [*17*]. During the balance study with stilbestrol, our patient received a high protein diet with a normal intake of calcium and phosphorus. The retention of nitrogen and bone minerals did not appear to be influenced by estrogen therapy. It is uncertain if the slightly decreased rate of phosphorus retention in the period after control was related in any way to the withdrawal of estrogen therapy. The theoretic phosphorus balance was in general agreement with the measured balance in the second study, presenting a considerable contrast to the findings of the first study.

Spontaneous repair of the femoral fracture in this patient suggested that bone healing could occur despite a prolonged deficiency of serum alkaline phosphatase. Spontaneous mineralization of bone has been reported in children with hypophosphatasia by Currarino et al. [*18*] and by Owen in a child who reached adult life [*13*]. Fraser [*2*] expressed the opinion that the radiologic improvement in the cases reported by Anspach and Clifton [*19*] and Schleshinger, Luder and Bodian [*20*] also was spontaneous. Furthermore, according to the published evidence, the serum alkaline phosphatase activity did not show any tendency to rise during bone healing in these cases. In contrast to this general finding, a pediatric patient reported on by Fraser and Laidlaw [*14*] and discussed in later reports [*2,21*] showed bone healing and an increase in serum alkaline when given cortisone. This occurred at a dosage of 37.5 mg. of cortisone per day after higher doses had failed to influence the serum alkaline phosphatase activity. This effect of cortisone therapy appeared to be definite in their case, as the alkaline phosphatase fell when cortisone was stopped and again rose with its reinstitution. Klein also noted a rise in serum alkaline phosphatase [*22*] in one patient. Despite a specific attempt to detect a similar response in our patient, administration of prednisone at three different dosage levels failed to influence the serum alkaline phosphatase

levels. Perhaps even the smallest dose, 15 mg. per day, was excessive in our patient, since Fraser's pediatric patient did not respond to the administration of 100 or 50 mg. of cortisone daily but did at a dose of 37.5 mg. The adult patient of Macey [*12*] showed a transient rise in serum alkaline phosphatase after bone grafting.

The level of serum alkaline phosphatase activity has been variably influenced by the administration of cortisone to normal human subjects or animals. Laron, Fortunato and Klein [*23*] showed that rats given cortisone in increasing doses exhibited increased serum alkaline phosphatase activity until the dose of cortisone was large enough to produce weight loss. Then, with increasing weight loss, the serum alkaline phosphatase fell progressively. The leukocytic alkaline phosphatase also was not influenced by prednisone therapy in our patient [*11*] although in normal subjects ACTH gel administered intramuscularly in doses of 90 to 120 units daily caused a fourfold increase in white blood cell alkaline phosphatase activity [*24*], with lesser increases after the administration of cortisone acetate or hydrocortisone. These demonstrations that alkaline phosphatase activity in serum and tissues can be stimulated by ACTH or adrenocorticoids are in apparent contradiction to the findings of heightened alkaline phosphatase activity in bone, serum and tissue after adrenalectomy [*25,26*]. In any event, no change in serum or leukocyte alkaline phosphatase was detected during steroid therapy in our patient.

The alkaline phosphatase activity has responded to the administration of estrogen in quite a variable fashion in different tissues and animals. Estrogens stimulated a marked increase in the alkaline phosphatase activity in tissues of the genital tract of rats and mice [*27,28,29*] but this effect was considerably reduced in guinea pigs and rabbits [*30*]. The alkaline phosphatase activity was also stimulated by estrogen therapy in the buccal mucosa of rats but not in the gingival mucosa [*31*]. The administration of estrogens exerted no stimulatory effect on renal alkaline phosphatase of mice [*32,33*] and caused a rise in hepatic alkaline phosphatase activity only when extremely potent preparations or large doses were employed [*33*]. Reifenstein and Albright [*17*] reported the failure of stilbestrol to lead to any rise in serum alkaline phosphatase in patients with osteoporosis of the postmenopausal, senile, disuse or Cushingoid types. In an acromegalic with osteoporosis, however, a rise in serum alkaline phosphatase from normal levels was noted during and after therapy with estradiol dipropionate [*34*]. No change in serum or tissue alkaline phosphatase activity (as determined in leukocytes) was detected during estrogen therapy in our patient.

SUMMARY

A diagnosis of hypophosphatasia of the type which occurs in adults was established in a thirty-six year old white man who suffered an incomplete femoral fracture after minimal trauma. The diagnosis was established on the basis of consistently low serum alkaline phosphatase values, apparent absence of alkaline phosphatase activity in leukocytes, and an abnormally high urinary excretion of phosphorylethanolamine.

In two prolonged metabolic balance studies during healing of the fracture it was noted that the patient was retaining calcium and phosphorus. The rate of retention of these minerals was not influenced by the administration of prednisone in three dosage levels or by stilbestrol. These drugs also failed to cause elevation of the low serum alkaline phosphatase, or to induce detectable alkaline phosphatase activity in leukocytes. The nitrogen balance varied with intake and the dosage of prednisone, and did not parallel the balance of calcium or phosphorus.

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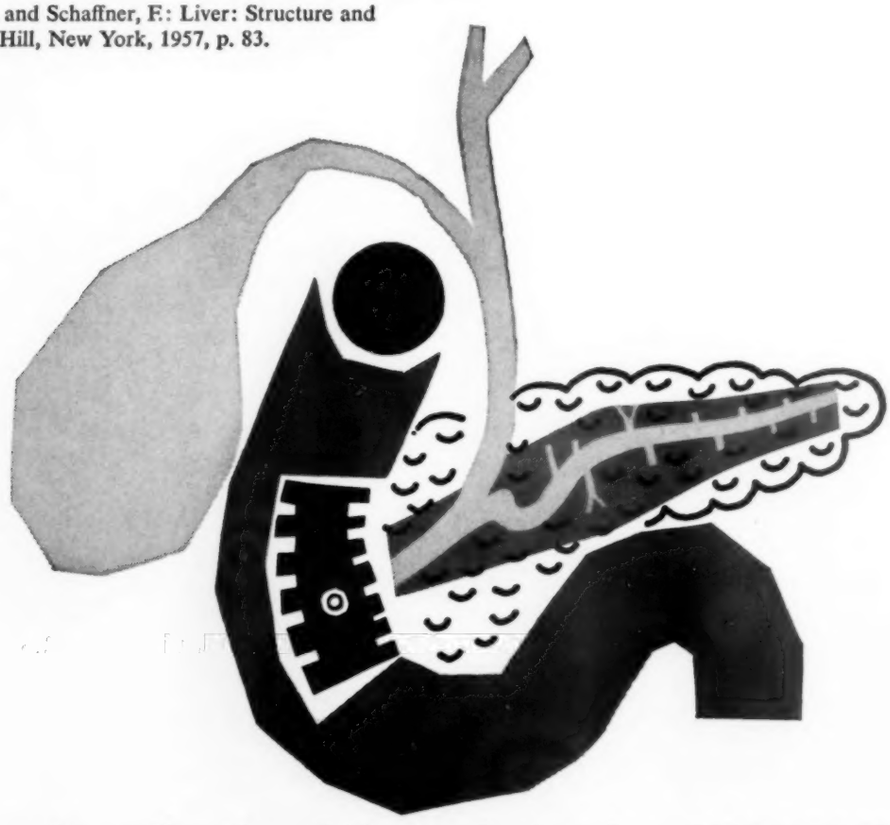
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In *figure #3,* the test tube at the left contains lipemic serum, while the one at the right contains clear, or normal serum. If serum examined after a 12-hour fasting period presents a milky appearance, this is a strong indication that the patient clears fat slowly and is a candidate for antilipemic therapy in an effort to check a potentially serious situation.

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Fig. 1

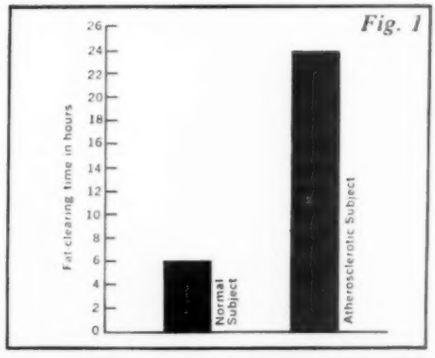


Fig. 2

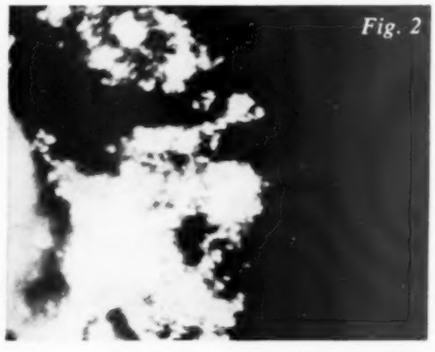
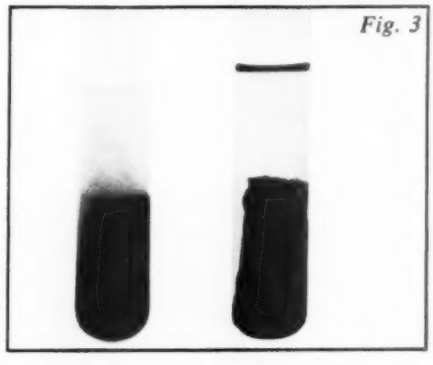


Fig. 3



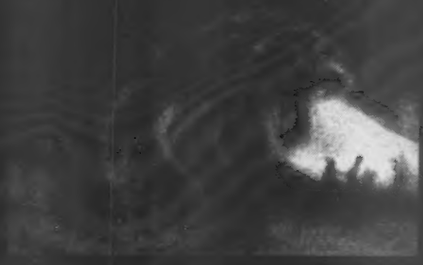
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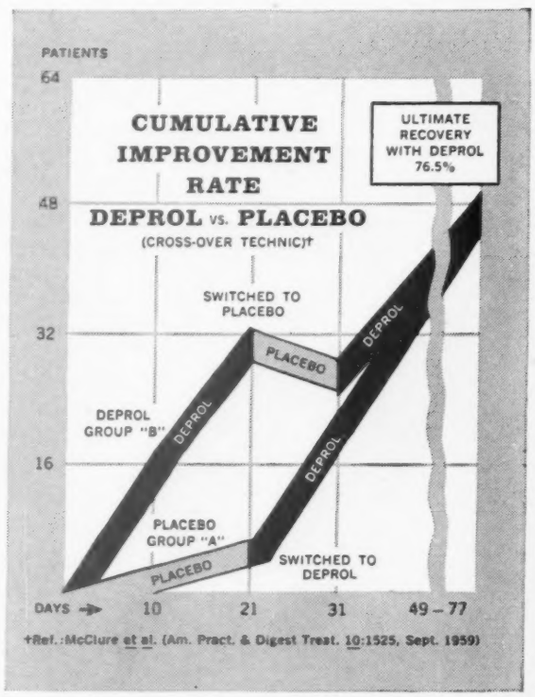
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BIBLIOGRAPHY *(11 clinical studies, 764 patients):*

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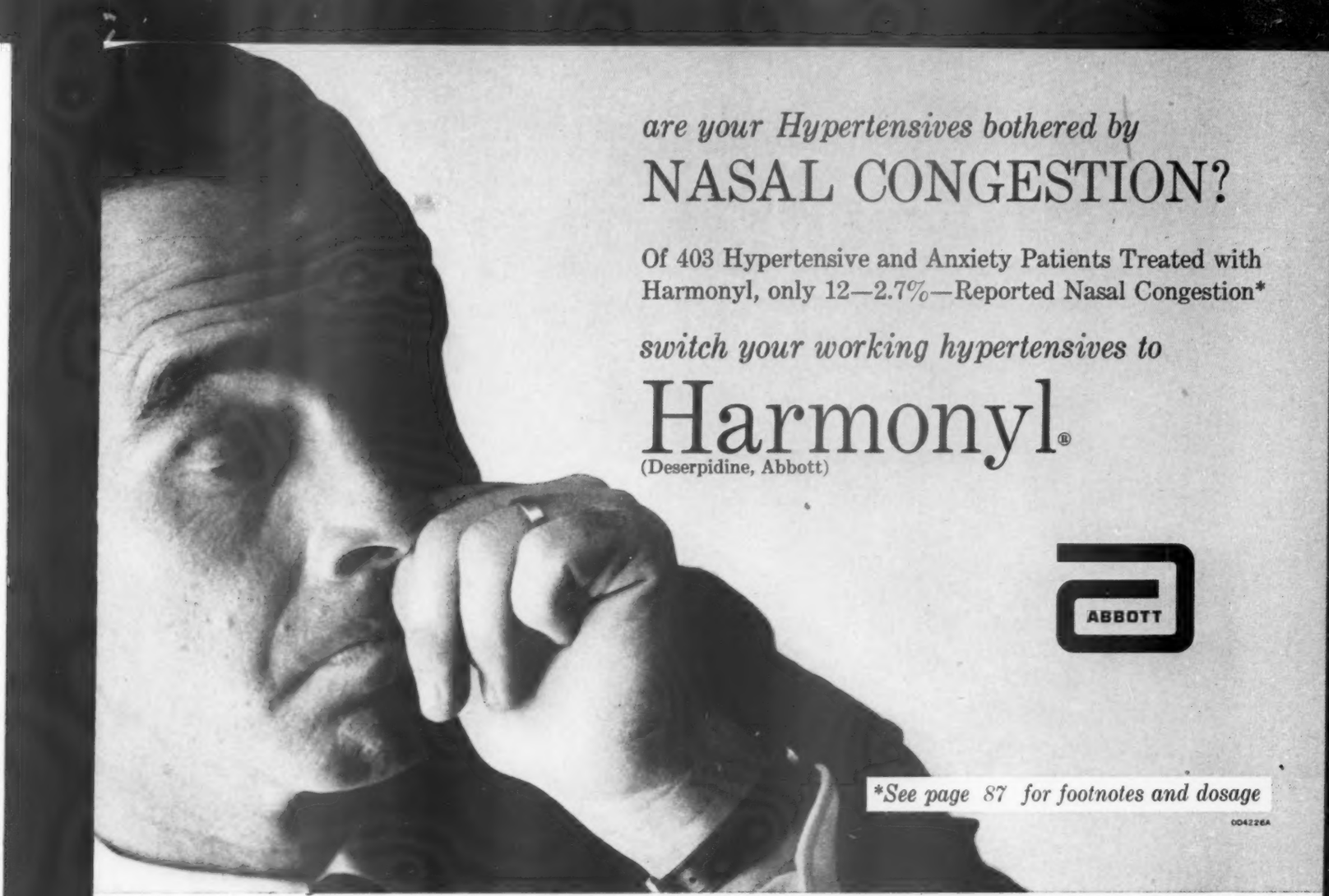
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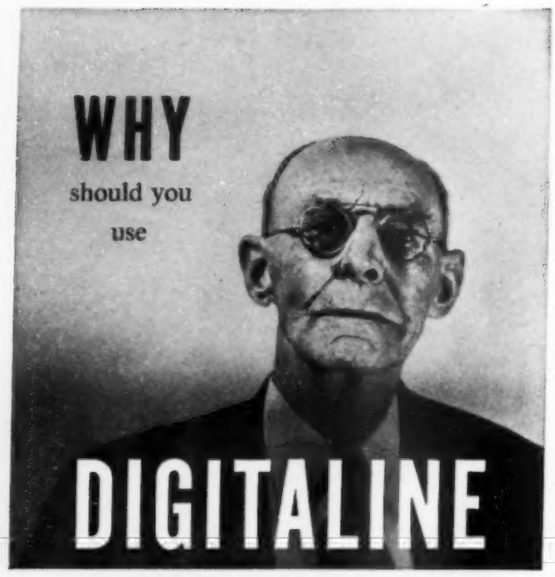
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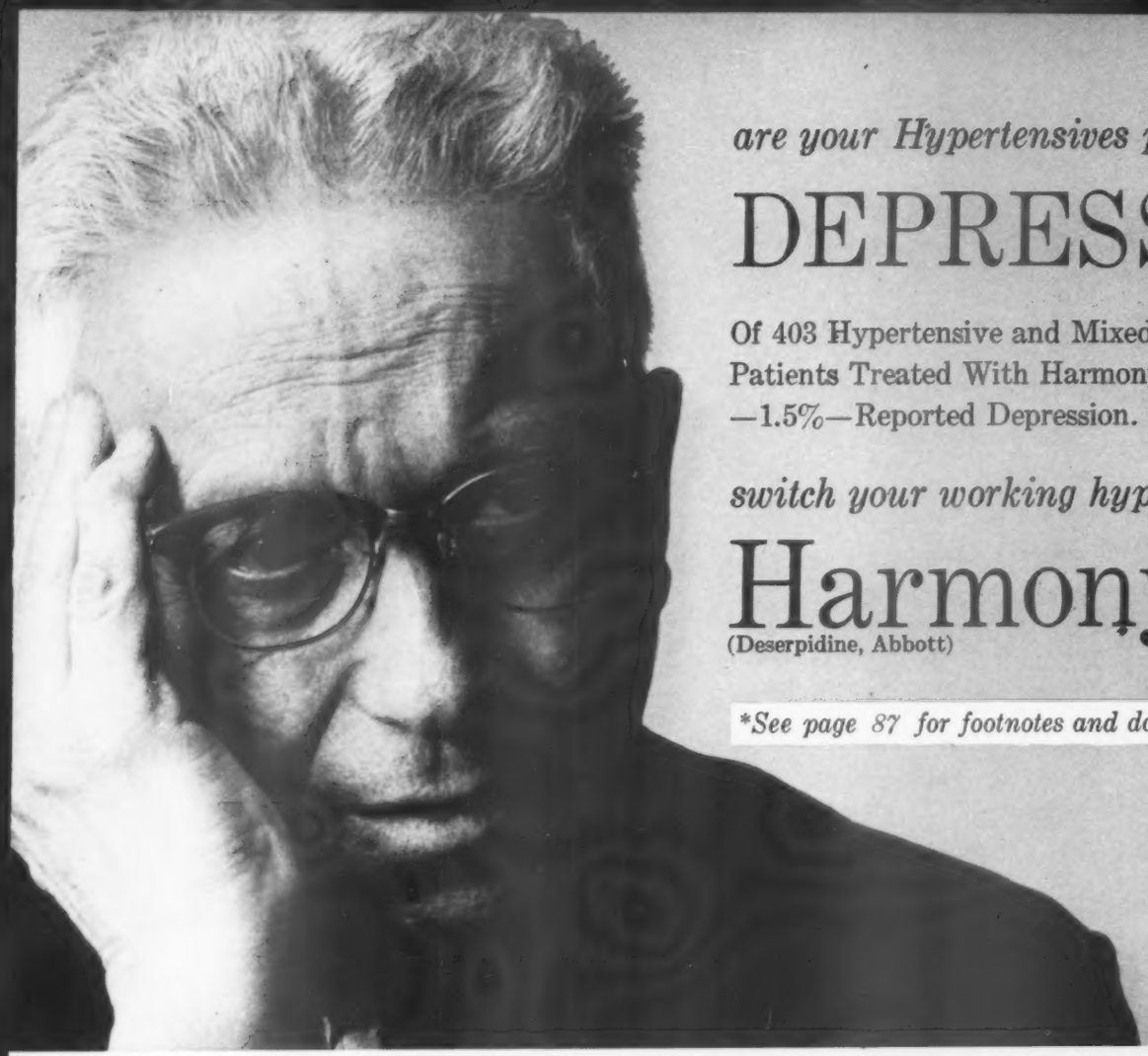
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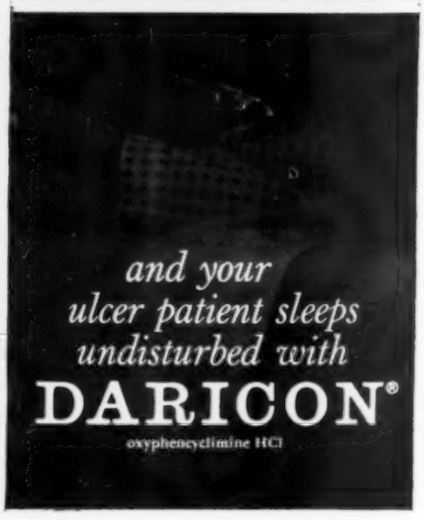
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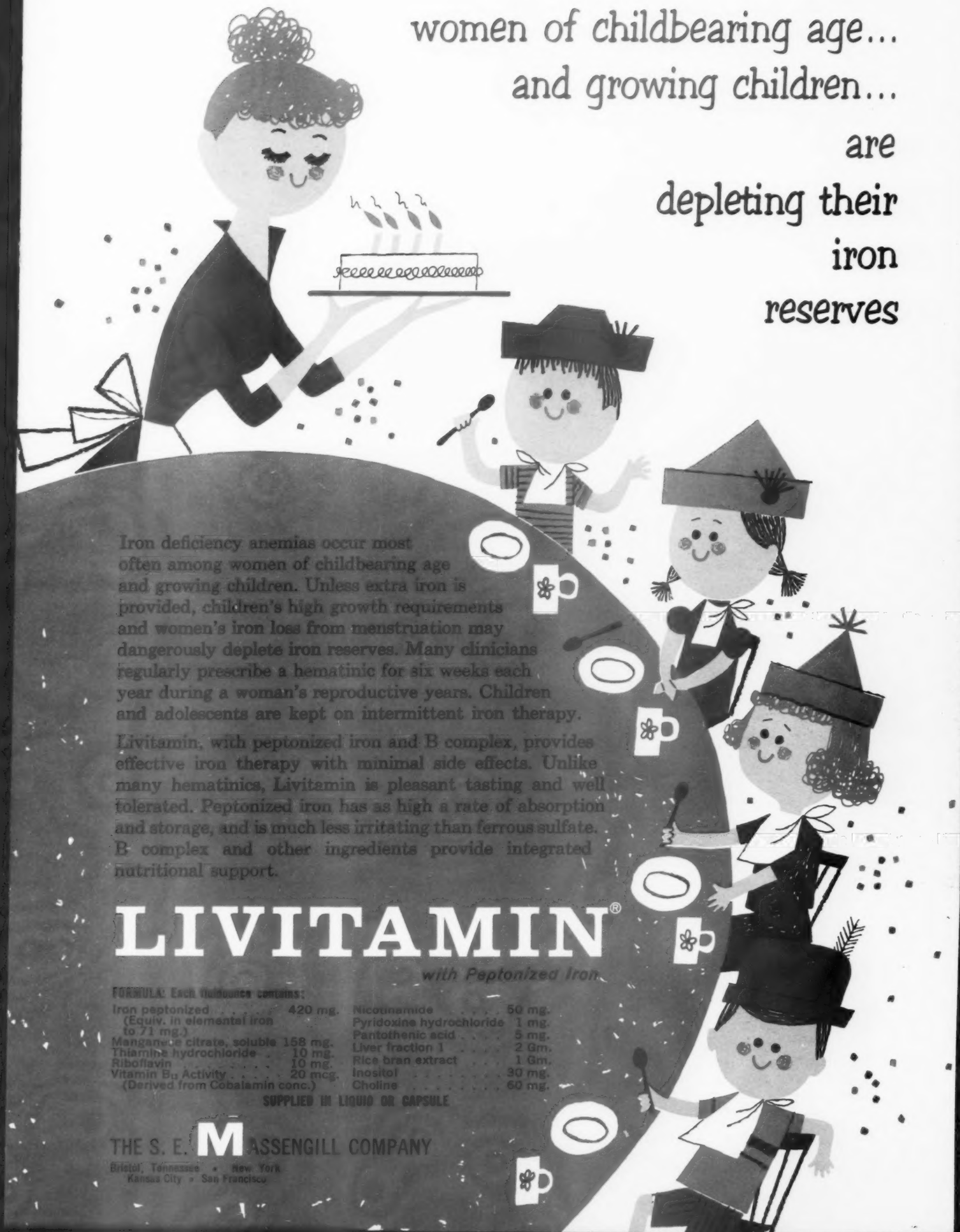
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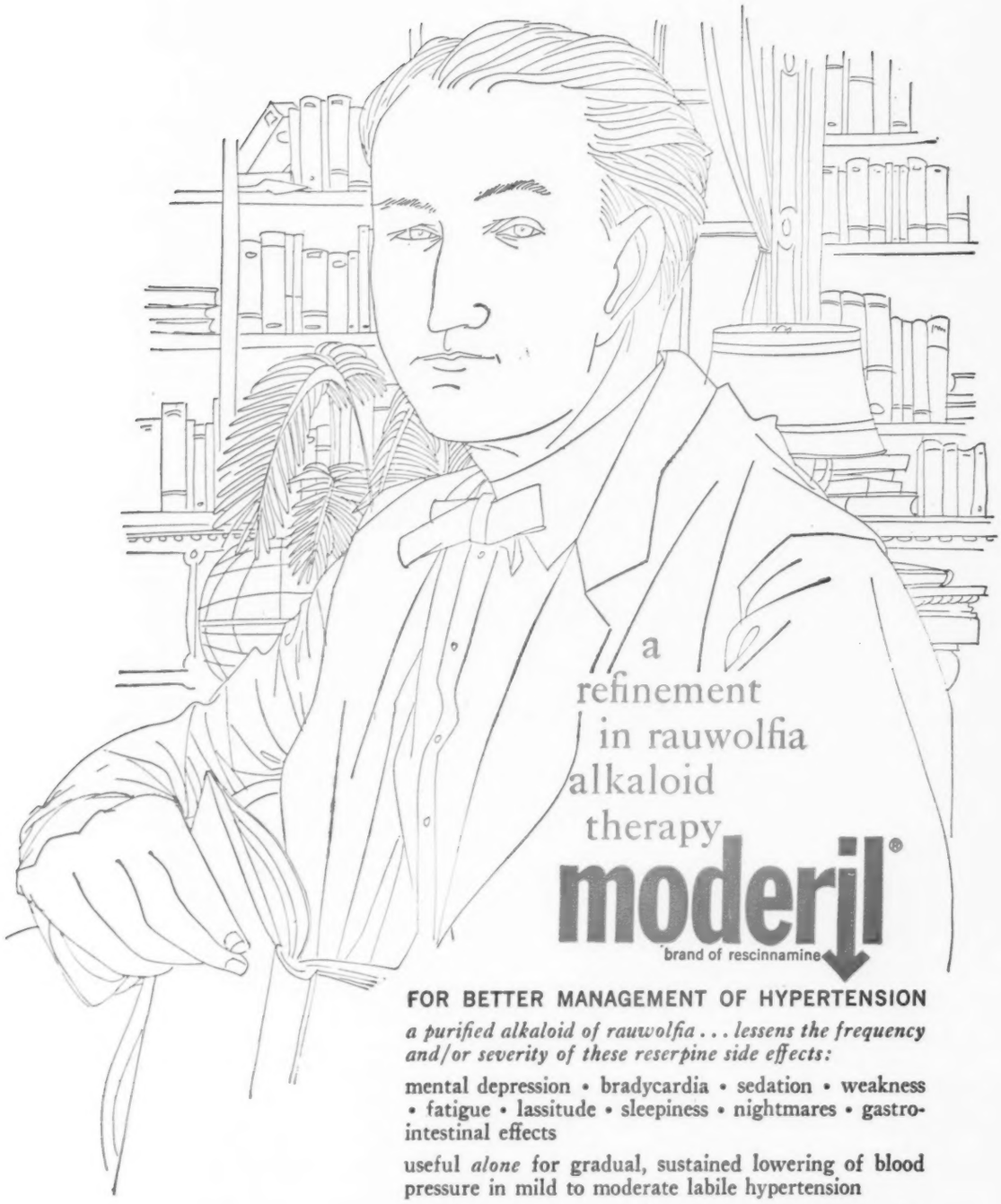


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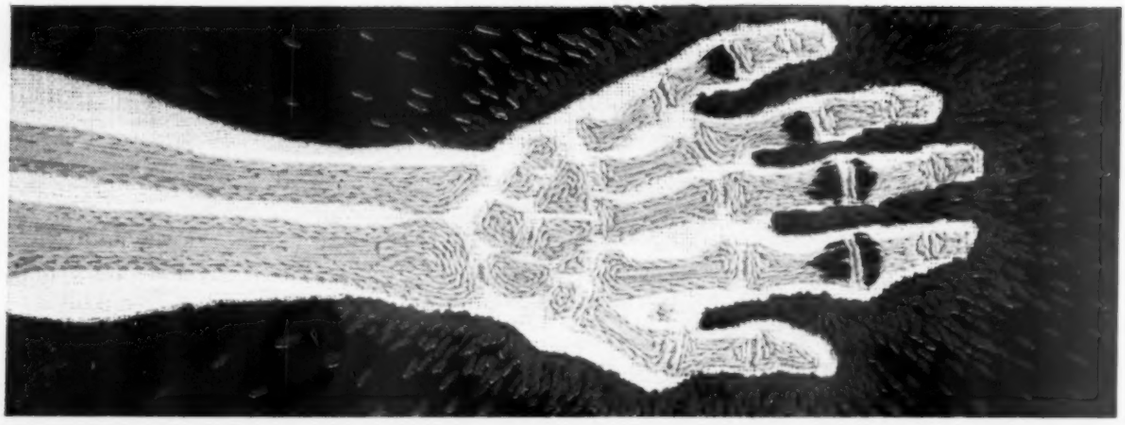
Dosage: 1 or 2 tablets t.i.d. at mealtime and 2 at bedtime.

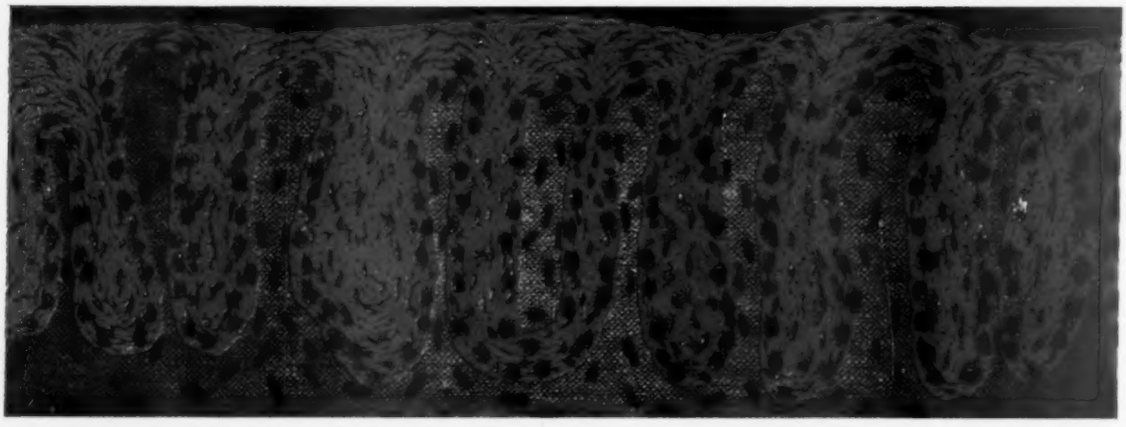
Milpath®

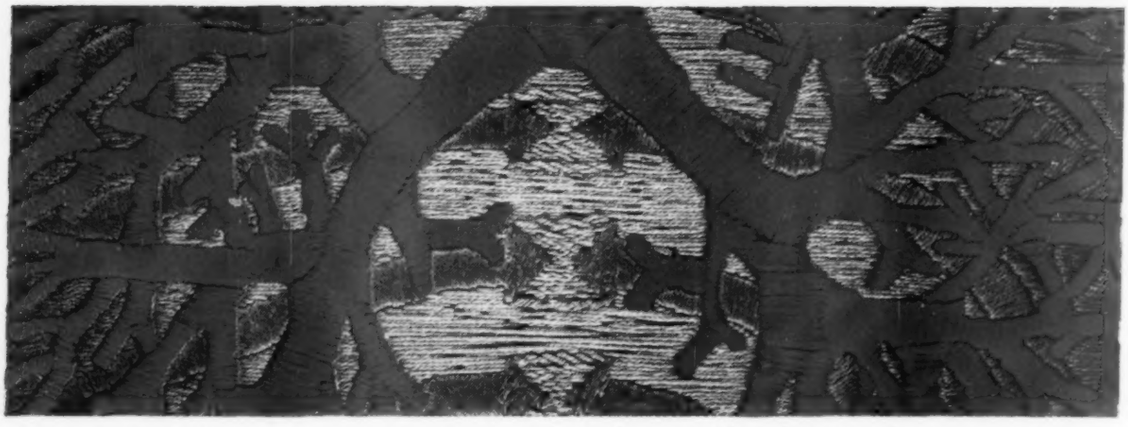
®Miltown + *anticholinergic*

WALLACE LABORATORIES *New Brunswick, N. J.*

a promise fulfilled







All corticosteroids provide symptomatic control in rheumatoid arthritis, inflammatory dermatoses, and bronchial asthma. They *differ* in the frequency and severity of side effects. Introduced in 1958, ARISTOCORT Triamcinolone bore the promise of high efficacy and relative safety. Physicians today recognize that the promise has been fulfilled . . . as evidenced by the high rate of refilled ARISTOCORT prescriptions.

Aristocort® Triamcinolone LEDERLE

Lederle LEDERLE LABORATORIES, A Division of AMERICAN CYANAMID COMPANY, Pearl River, N.Y.

NOW...
A DRUG THAT LOWERS CHOLESTEROL LEVELS AS MUCH AS 200 mg.%
WITH NO ANNOYING SIDE EFFECTS IN 80% OF PATIENTS...AND NO DIETARY RESTRICTIONS

NICALEX*

TABLETS aluminum nicotinate Walker

New NICALEX reduces blood cholesterol levels as much as 200 mg. % with no flushing, itching or gastrointestinal disturbance in 80% of patients.[1-4] Significant reductions have been obtained in close to 90% of hypercholesteremic patients to date.[1-4] Lowered cholesterol levels can be maintained indefinitely with little or no discomfort to most patients. And there is no need to restrict the diet throughout therapy.

A newly synthesized salt of nicotinic acid, NICALEX is "...as effective in reducing blood cholesterol as plain nicotinic acid...."[5] But unlike the older therapy, which produces vasomotor and gastrointestinal side effects in the vast majority of patients, NICALEX is characterized by a markedly reduced incidence of unpleasant reactions.[1-5]

NICALEX is so well tolerated because it is hydrolyzed *slowly* and *uniformly* in the gastrointestinal tract into aluminum hydroxide, an effective buffering agent, plus active nicotinic acid. Thus, a sustained cholesterol-lowering action can be readily maintained with a lower incidence of unwanted effects.

Dosage: 2 to 4 tablets t.i.d., with or after meals. Each tablet contains aluminum nicotinate Walker equivalent in activity to 500 mg. of nicotinic acid.

Supplied: Bottles of 100 and 1000.

References: **1.** Tandowsky, R. M.: Personal communication. **2.** Parsons, W. B.: *Curr. Therapeut. Res.* 2:137 (May) 1960. **3.** Thompson, C. E.: Personal communication. **4.** Biben, L. H.; Kurstin, W., and Protas, M.: Personal communication. **5.** Hobbs, T. G.: Personal communication.

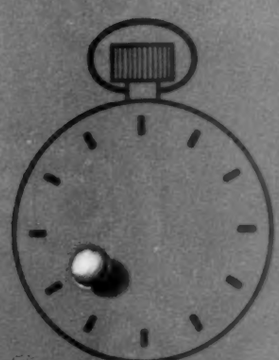
*PAT. PENDING

Walker LABORATORIES, INC., MOUNT VERNON, N. Y.

a NEW perspective in the control of anxiety

---

now–only one tablet daily
calms without drowsiness
all…day…long



economical

Permitil®

Fluphenazine dihydrochloride

Chronotabs®

sustained-action tablets

Permitil approaches the ideal in anti-anxiety therapy

■ A significantly wider range of anxiety symptoms amenable to therapy

PERMITIL "mitigates apathy, indifference, inertia and anxiety-induced fatigue."[1]

■ A higher percentage of favorable results

Significant improvement in over 90% of patients treated.[2,3]

■ A lower incidence of side effects

At recommended dosage levels, virtual freedom from autonomic, endocrine or neuromuscular (extrapyramidal) side effects.

■ A greater specificity of action

Patients become calm without drowsiness, mental acuity is sharpened and normal drive is restored.

And now ■ The simplest dosage schedule of all

In the large majority of adults, only one PERMITIL CHRONOTAB, taken upon arising, controls anxiety and anxiety-induced symptoms *all day long*.

Sig: One Permitil Chronotab (1 mg.) in the morning

Side effects from PERMITIL, at the recommended dosage, have been observed infrequently or not at all. PERMITIL, as with other phenothiazines, is contraindicated in severely depressed states. *Complete information concerning the use of this drug is available on request.*

PERMITIL CHRONOTABS, 1 mg., bottles of 30. Also available PERMITIL TABLETS, 0.25 mg., bottles of 50.

CHRONOTAB  is White's sustained-action tablet.

REFERENCES: 1. Ayd, F. J., Jr.: Current Therap. Res. 1:41, 1959. 2. Recent compilation of case reports received by the Medical Department, White Laboratories, Inc. 3. Ernst, E. M.: Clin. Med. (In press). Additional bibliography: Bodi, T., et al.: Clin. Res. 8:72, 1960. Dunlop, E.: Personal communication. Grimaldi, R.: Presented at Annual Congress of Pan-American Medical Association, May 6, 1960, Mexico City. Olson, J., and Carsley, S. H.: Personal communication.

White WHITE LABORATORIES, INC., KENILWORTH, NEW JERSEY

another patient with hypertension?





indicated in all degrees of hypertension

effective by itself in most hypertensives

HYDROPRES*

HYDRODIURIL® (HYDROCHLOROTHIAZIDE) with RESERPINE

HYDROPRES can be used:

- *alone* **(In most patients, HYDROPRES is the only antihypertensive medication needed.)**
- *as basic therapy, adding other drugs if necessary* **(Should other antihypertensive agents need to be added, they can be given in much lower than usual dosage so that their side effects are often strikingly reduced.)**
- *as replacement therapy, in patients now treated with other drugs* **(In patients treated with rauwolfia or its derivatives, HYDROPRES can produce a greater antihypertensive effect. Moreover, HYDROPRES is less likely to cause side effects characteristic of rauwolfia, since the required dosage of reserpine is usually less when given in combination with HydroDIURIL than when given alone.)**

HYDROPRES-25
25 mg. HydroDIURIL, 0.125 mg. reserpine.
One tablet one to four times a day.

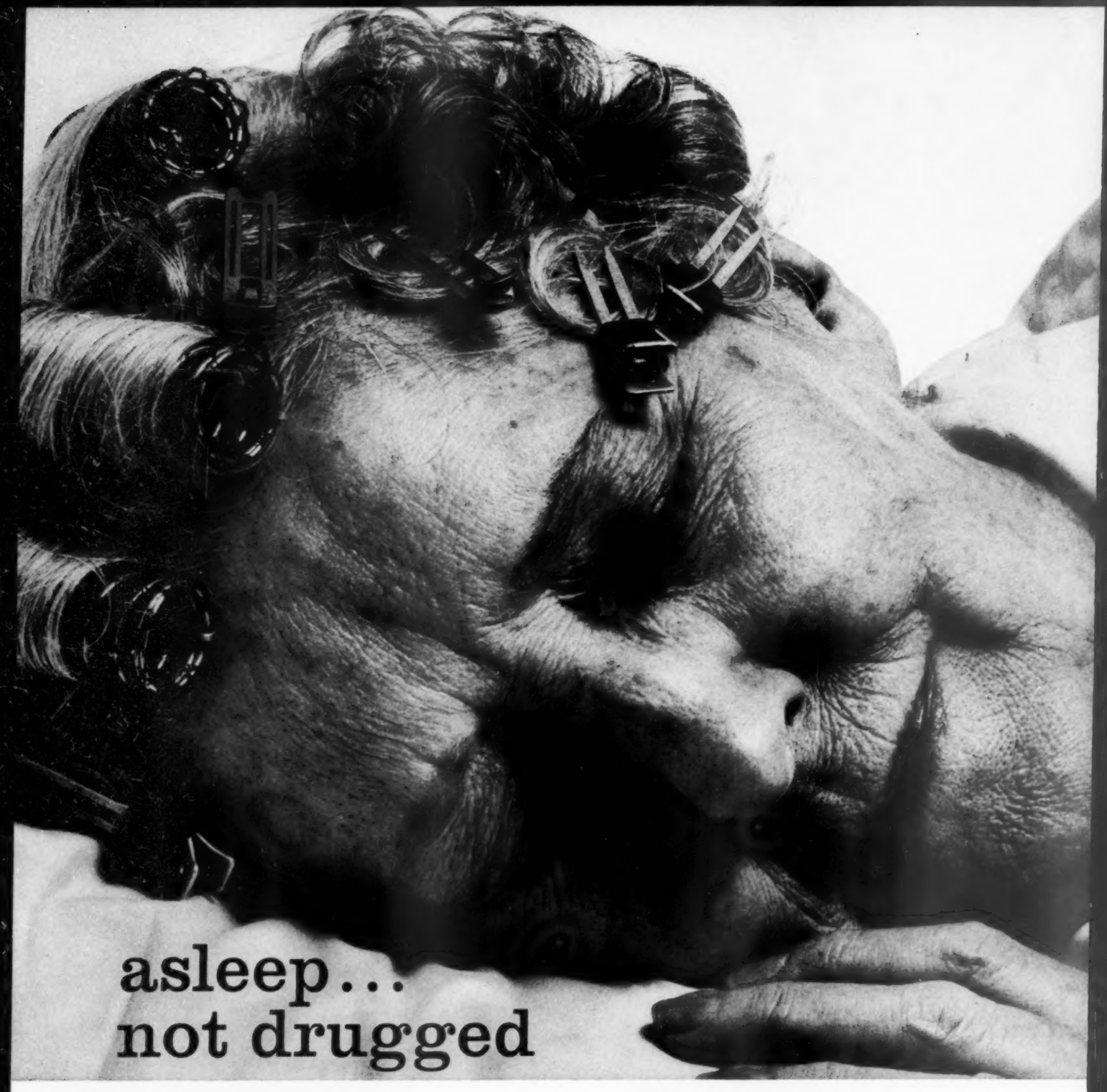
HYDROPRES-50
50 mg. HydroDIURIL, 0.125 mg. reserpine.
One tablet one or two times a day.

If the patient is receiving ganglion blocking drugs or hydralazine, their dosage must be cut in half when HYDROPRES is added.

For additional information, write Professional Services, Merck Sharp & Dohme, West Point, Pa.

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For a night of deep, refreshing sleep and a lively awakening... Noludar 300... one capsule at bedtime promises 6 to 8 hours of undisturbed sleep without risk of habituation, without barbiturate "hangover," toxicity or even minor side effects. Try Noludar 300 for your next patient with a sleep problem. One capsule at bedtime. Chances are she'll tell you

"I slept like a log"

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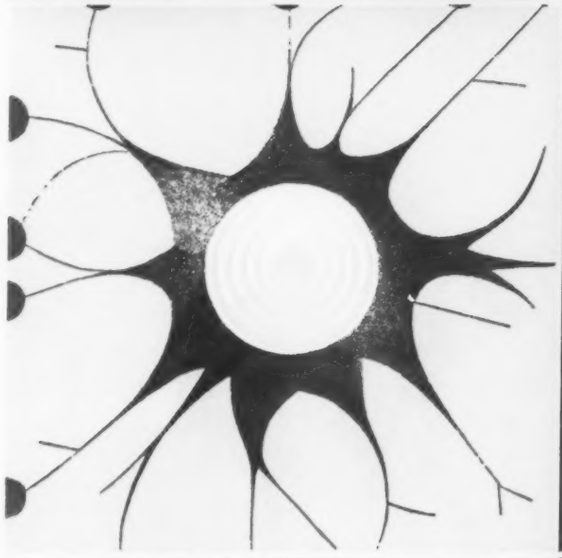
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whenever depression complicates the picture

Tofrānil®

brand of imipramine HCl



hastens recovery

Geigy

In many seemingly mild physical disorders an element of depression plays an insidious etiologic or complicating role.

Because of its efficacy as an antidepressant, coupled with its simplicity of usage, Tofrānil is admirably adapted to use in the home or office in these milder "depression-complicated" cases.

It is always wise to recognize that depression may be an underlying factor... that Tofrānil may speed recovery in "hypochondriasis"; in convalescence when recovery is inexplicably prolonged; in chronic illness with dejection; in the menopausal patient whose emotional disturbances resist hormone therapy; and in many other comparable situations in which latent depression may play a part.

Detailed Literature Available on Request.

Tofrānil®, brand of imipramine hydrochloride, tablets of 25 mg. Ampuls for intramuscular administration, 25 mg. in 2 cc. of solution.

Geigy, Ardsley, New York

160-60

first choice for MIGRAINE
recurrent, throbbing "sick" headaches...

CAFERGOT®



When the headache is associated with nervous tension and G.I. disturbance:

CAFERGOT P-B TABLETS: **ergotamine tartrate 1 mg., caffeine 100 mg., Bellafoline 0.125 mg., pentobarbital sodium 30 mg. Dosage: 2 at first sign of attack; if needed, 1 additional tablet every ½ hour until relieved (maximum 6 per attack).**

CAFERGOT P-B SUPPOSITORIES: **ergotamine tartrate 2 mg., caffeine 100 mg., Bellafoline 0.25 mg., pentobarbital sodium 60 mg. Dosage: 1 as early as possible in attack; second in 1 hour, if needed (maximum 2 per attack).**

CAFERGOT TABLETS: **ergotamine tartrate 1 mg., caffeine 100 mg. Dosage: same as Cafergot P-B Tablets.**

CAFERGOT SUPPOSITORIES: **ergotamine tartrate 2 mg., caffeine 100 mg. Dosage: same as Cafergot P-B Suppositories.**

For a new brochure on Migraine and Tension Headaches, reviewing clinical reports on diagnosis and therapy, write: Sandoz, Hanover, N. J.

SANDOZ

CLINICAL REMISSION
IN A "PROBLEM" ARTHRITIC

In rheumatoid arthritis with serious corticoid side effects. Following profound weight loss and acute g.i. distress on prednisolone, a 45-year-old bookkeeper with a five-year history of severe arthritis was started on DECADRON, 1 mg./day. Dosage was promptly reduced to 0.5 mg./day. After ten months on DECADRON, she gained back eleven pounds, feels very well, and had no recurrence of stomach symptoms. She is in clinical remission.*

New convenient b.i.d. alternate dosage schedule: the degree and extent of relief provided by DECADRON allows for b.i.d. maintenance dosage in many patients with so-called "chronic" conditions. Acute manifestations should first be brought under control with a t.i.d. or q.i.d. schedule.

Supplied: As 0.75 mg. and 0.5 mg. scored, pentagon-shaped tablets in bottles of 100. Also available as Injection DECADRON Phosphate. Additional information on DECADRON is available to physicians on request. DECADRON is a trademark of Merck & Co., Inc.

*From a clinical investigator's report to Merck Sharp & Dohme.

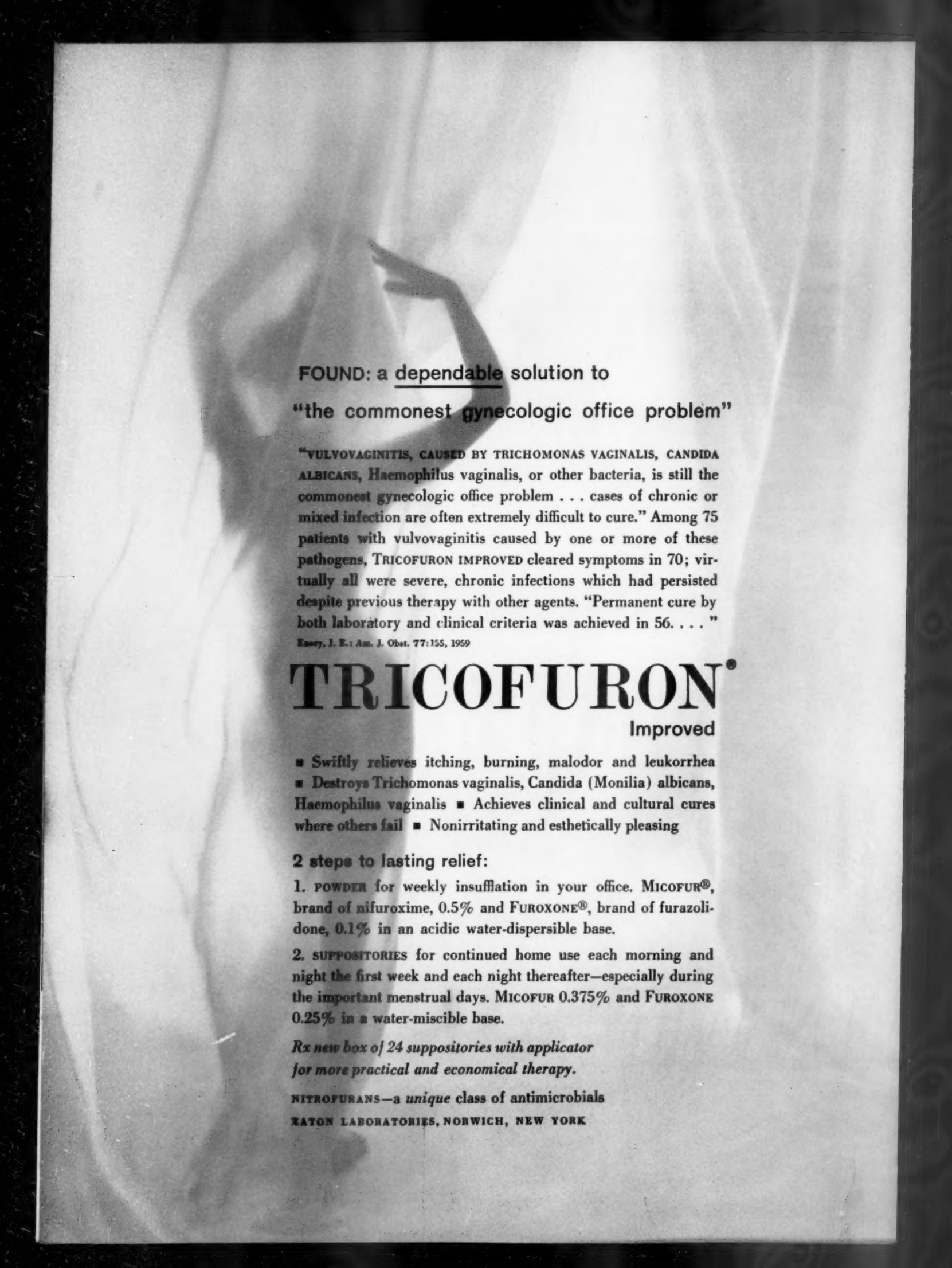
Decadron®

Dexamethasone

TREATS MORE PATIENTS MORE EFFECTIVELY

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FOUND: a dependable solution to

"the commonest gynecologic office problem"

"VULVOVAGINITIS, CAUSED BY TRICHOMONAS VAGINALIS, CANDIDA ALBICANS, Haemophilus vaginalis, or other bacteria, is still the commonest gynecologic office problem . . . cases of chronic or mixed infection are often extremely difficult to cure." Among 75 patients with vulvovaginitis caused by one or more of these pathogens, TRICOFURON IMPROVED cleared symptoms in 70; virtually all were severe, chronic infections which had persisted despite previous therapy with other agents. "Permanent cure by both laboratory and clinical criteria was achieved in 56. . . . "

Emery, J. E.: Am. J. Obst. 77:155, 1959

TRICOFURON®

Improved

■ Swiftly relieves itching, burning, malodor and leukorrhea ■ Destroys Trichomonas vaginalis, Candida (Monilia) albicans, Haemophilus vaginalis ■ Achieves clinical and cultural cures where others fail ■ Nonirritating and esthetically pleasing

2 steps to lasting relief:

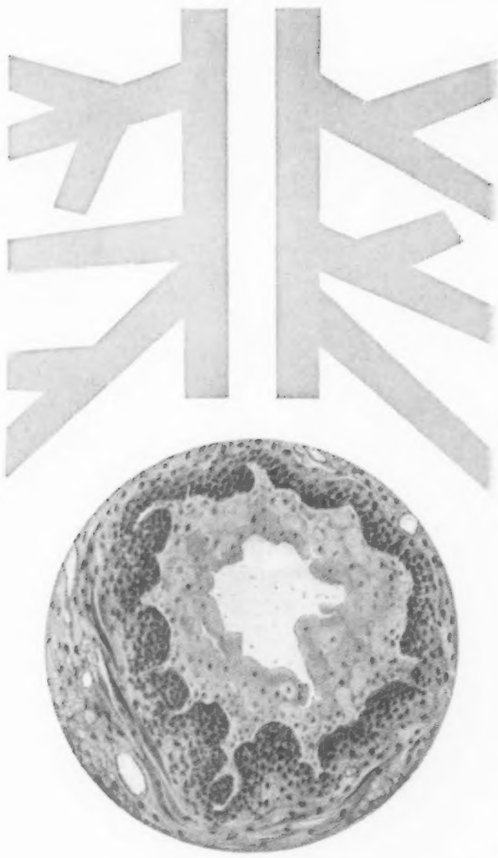
1. POWDER for weekly insufflation in your office. MICOFUR®, brand of nifuroxime, 0.5% and FUROXONE®, brand of furazolidone, 0.1% in an acidic water-dispersible base.

2. SUPPOSITORIES for continued home use each morning and night the first week and each night thereafter—especially during the important menstrual days. MICOFUR 0.375% and FUROXONE 0.25% in a water-miscible base.

Rx new box of 24 suppositories with applicator for more practical and economical therapy.

NITROFURANS—a *unique* class of antimicrobials

EATON LABORATORIES, NORWICH, NEW YORK



Report on a recent clinical study. **Condition:** several principal respiratory allergies. **Age Range:** one to seventy-three years.

Treatment: NORISODRINE® SYRUP WITH CALCIUM IODIDE
(ISOPROTERENOL SULFATE, ABBOTT)

Cough, bronchitis, tracheobronchitis, secondary bronchospasm in virus infection, and outright asthma: such were the allergies of patients administered new Norisodrine Syrup in a recent study.[1]

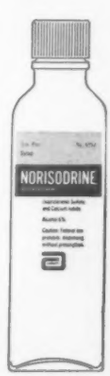
Of the 150 patients treated—ranging in age from one to seventy-three years—*133 reported good to excellent results.* (Only three patients reduced dosage due to tachycardia.)

Conclusions: "Norisodrine Syrup diminished cough, brought about easy expectoration of mucus from the bronchial tree, lessened tightness in the chest, improved respiration."

In prescribing Norisodrine Syrup, you'll be able to see for yourself just how well this unique preventive agent can work with your allergy patients—even those whose condition may be long-standing.

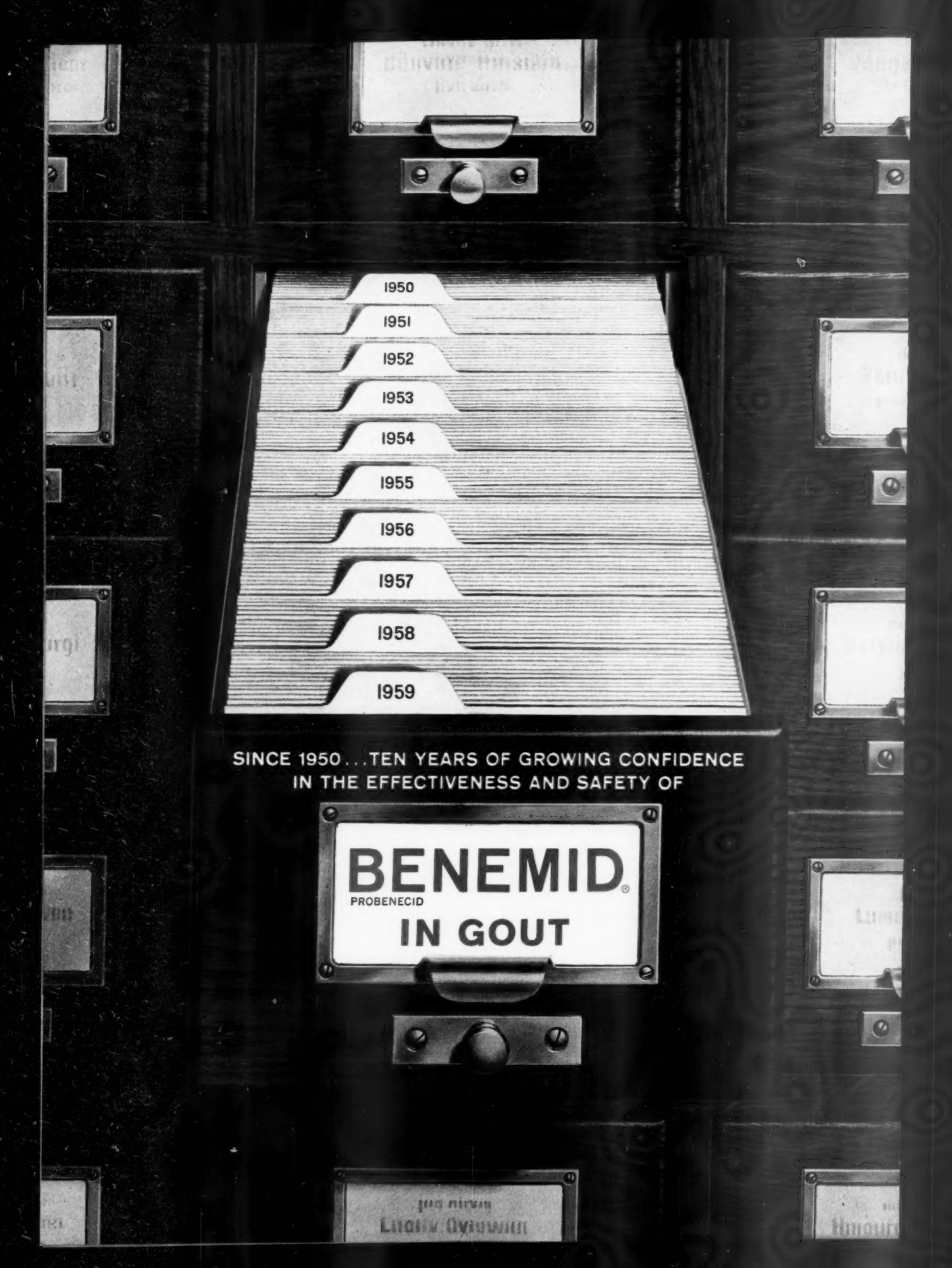
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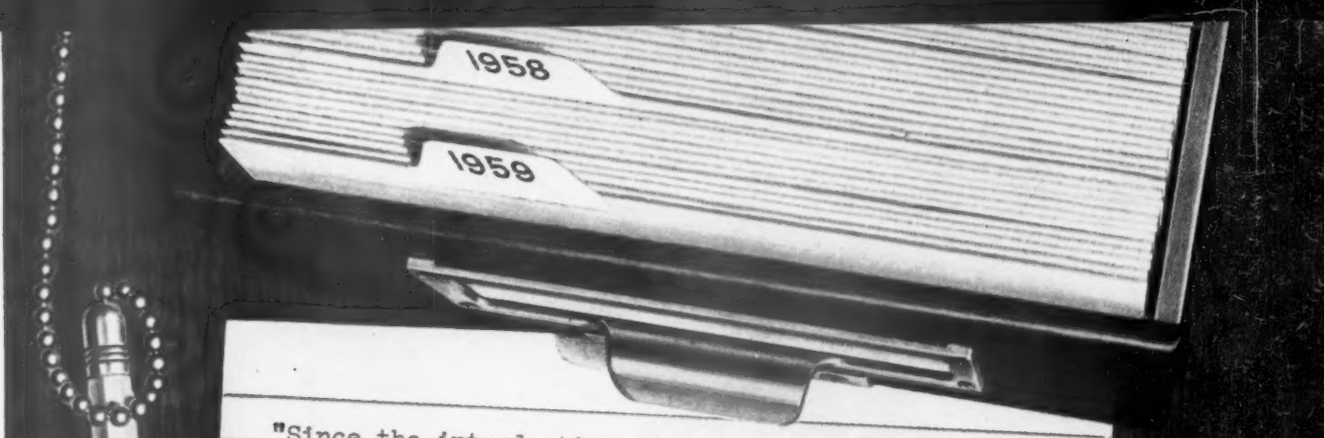
007251



Norisodrine Syrup's pleasant mint flavor will be appreciated by your younger patients, and those likely to receive long-term therapy.

[1]Frohman; I. P.; Washington, D.C.; communication to the Medical Department, Abbott Laboratories, Jan. 16, 1960.


1950
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SINCE 1950 . . . TEN YEARS OF GROWING CONFIDENCE
IN THE EFFECTIVENESS AND SAFETY OF
BENEMID®
PROBENECID
IN GOUT



"Since the introduction of probenecid [BENEMID] into clinical medicine...a great deal of justifiable enthusiasm has been evidenced and numerous reports on the use of this drug have appeared....All patients who have gout should be offered prolonged therapy with a safe uricosuric agent such as probenecid...."1

1. Bartels, E. C., and Matossian, G. S.: Gout: Six-Year Follow-Up on Probenecid (BENEMID) Therapy, Arthritis and Rheumatism 2:193, June 1959.

BENEMID is "remarkably free from toxic side reaction....Patients tolerate the drug well."2

2. Lockie, L. M., and Talbott, J.: Does Your Patient Have Gout?, Scientific Exhibit, American Medical Association, New York City, June 3-7, 1957.

"Probenecid [BENEMID] is the drug of choice as a uricosuric agent. Treatment should be instituted with 0.25 Gm. given twice daily for one week, then increased to 0.5 Gm. twice daily thereafter, without interruption."3

3. Kron, K. M., Hermann, I. F., Smith, R. T., and Richards, J. C.: Which Rheumatic Disease?, Scientific Exhibit, American Medical Association, Atlantic City, June 8-12, 1959.

Supply: BENEMID* probenecid, 0.5 Gm. tablets, bottles of 100 and 1000.

Also available: CoLBENEMID,* 0.5 mg. colchicine and 0.5 Gm. BENEMID. Bottles of 100.

For additional information, write Professional Services, Merck Sharp & Dohme, West Point, Pa.

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"from carcinomatosis to car sickness"



for faster, more prolonged and effective antiemetic action in the entire range of emetic situations

Tigan

NEW 250 mg CAPSULES

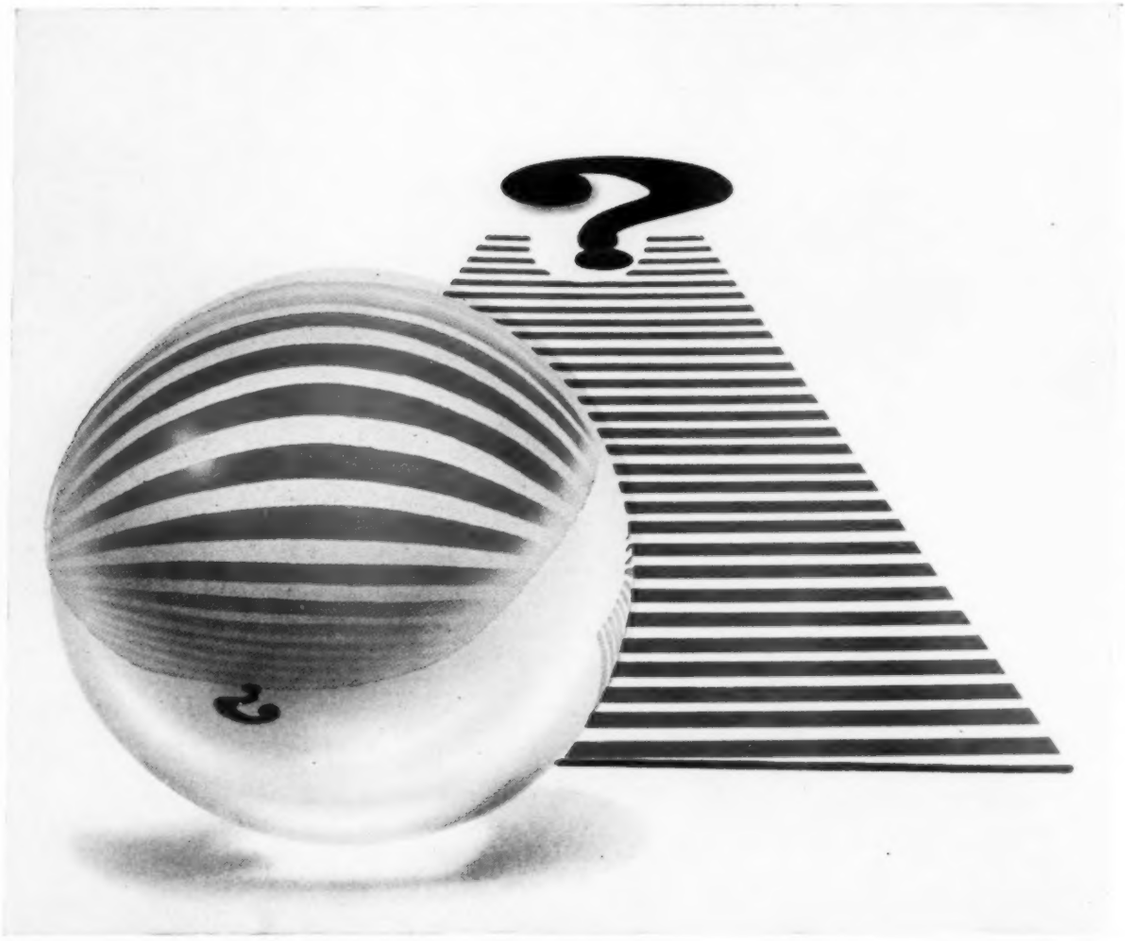
without phenothiazine risks
without the limitations
of antihistamines

Available: Capsules, blue, 250 mg—bottles of 50.
Also available as: 100 mg Capsules, blue and white.
Ampuls, 2 cc (100 mg/cc).
Vials, 20 cc (100 mg/cc). Suppositories, 200 mg.

TIGAN® Hydrochloride—4-(2-dimethylaminoethoxy)-N-(3,4,5-trimethoxybenzoyl) benzylamine hydrochloride

Consult literature and dosage information, available on request, before prescribing.

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what lurks beyond the broad spectrum?

Broad spectrum antibiotics provide the best means of combating pathogenic organisms which range all the way from large protozoa through gram-negative and gram-positive bacteria to certain viruses at the far end of the spectrum.

But beyond the spectrum lurk pathogenic fungi. It is increasingly apparent that fungal superinfections may occur during or after a course of broad spectrum antibiotics.[1,2] Long term debilitating diseases, diabetes, pregnancy, corticosteroid therapy, high or prolonged antibiotic dosage, and other causes may predispose to fungal superinfections.[1,3,4]

Mysteclin-V controls infection and prevents superinfection. It makes a telling assault on bacterial infections and, in addition, prevents monilial overgrowth.[2,5-8] Mysteclin-V is a combination of tetracycline phosphate complex for reliable control of most infections encountered in daily practice, and Mycostatin, the safe antifungal antibiotic. When you prescribe Mysteclin-V, you provide "broad spectrum therapy" plus extra protection that extends beyond the spectrum of ordinary antibiotics.

In pediatrics: Mysteclin-F for Aqueous Drops and Mysteclin-F for Syrup are phosphate-potentiated tetracycline combined with the new antifungal antibiotic, Fungizone (amphotericin B). They provide good-tasting, fruit-flavored aqueous liquids for your pediatric patients.

Supplied: Mysteclin-V Capsules (250 mg./250,000 u.); Half-strength Capsules (125 mg./125,000 u.); Mysteclin-F for Syrup (125 mg./25 mg. per 5 cc.); for Aqueous Drops (100 mg./20 mg. per cc.)

References: 1. Dowling, H. F.: Postgrad. Med. *23*:594 (June) 1958. 2. Gimble, A. I.; Shea, J. G., and Katz, S.: Antibiotics Annual 1955-1956 New York, Medical Encyclopedia Inc., 1956, p. 676. 3. Long, P. H., in Kneeland, Y., Jr., and Wortis, S. B.: Bull. New York Acad. Med. *33*:552 (Aug.) 1957. 4. Rein, C. R.; Lewis, L. A., and Dick, L. A.: Antibiotic Med. & Clin. Ther. *4*:771 (Dec.) 1957. 5. Stone, M. L., and Mersheimer, W. L.: Antibiotics Annual 1955-1956, New York, Medical Encyclopedia Inc., 1956, p. 862. 6. Campbell, E. A.; Prigot, A., and Dorsey, G. M.: Antibiotic Med. & Clin. Ther. *4*:817 (Dec.) 1957. 7. Chamberlain, C.; Burros, H. M., and Borromeo, V.: Antibiotic Med. & Clin. Ther. *5*:521 (Aug.) 1958. 8. From, P., and Alli, J. H.: Antibiotic Med. & Clin. Ther. *5*:639 (Nov.) 1958.

Mysteclin-V

Tetracycline Phosphate Complex (Sumycin) and Nystatin (Mycostatin)

SQUIBB *Squibb Quality—the Priceless Ingredient*

'MYSTECLIN'®, 'SUMYCIN'®, 'MYCOSTATIN'®, AND 'FUNGIZONE'® ARE SQUIBB TRADEMARKS.

COUMADIN®

the proven anticoagulant

FOR ORAL, INTRAVENOUS OR INTRAMUSCULAR USE

Over 60 published papers since 1953



~~101,000,000~~

Over ~~90,000,000~~ *doses administered to date*



COUMADIN is the *original* and *only* warfarin responsible for establishing this drug as closely approaching the ideal anticoagulant.[1,2]

Full range of oral and parenteral dosage forms—COUMADIN® [warfarin sodium] is available as: *Scored tablets*—2 mg., lavender; 5 mg., peach; 7½ mg., yellow; 10 mg., white; 25 mg., red. Single Injection Units—one vial, 50 mg., and one 2-cc. ampul Water for Injection; one vial, 75 mg., and one 3-cc. ampul Water for Injection.

Average Dose Initial, 40-60 mg. For elderly and/or debilitated patients, 20-30 mg.

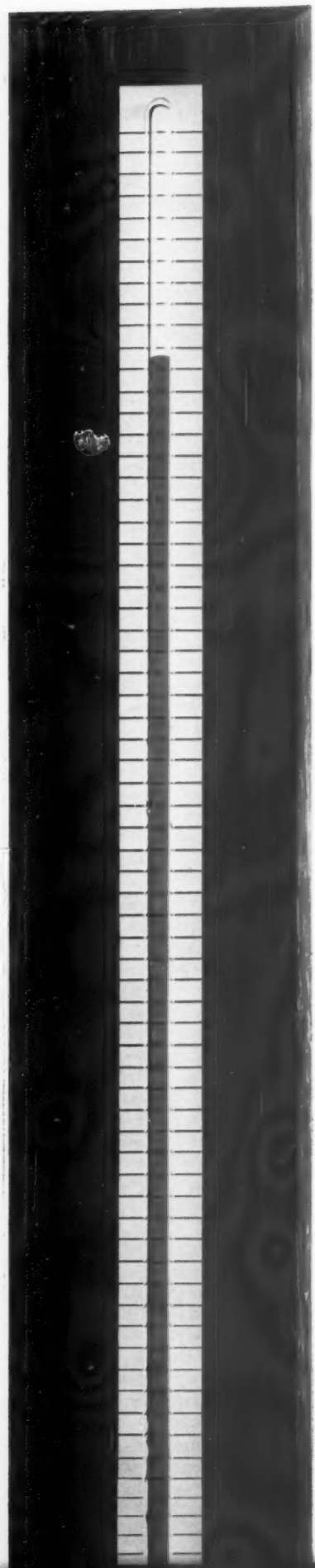
Maintenance, 5-10 mg. daily, as indicated by prothrombin time determinations.

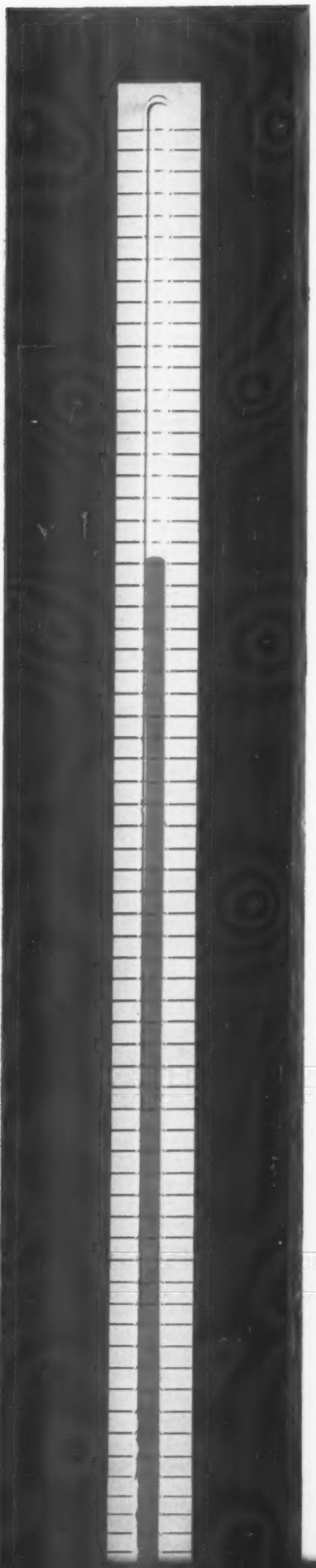
1. Baer, S., et al.: J.A.M.A. 167:704, June 7, 1958.
2. Modern, K. M.: Disease-a-Month, Chicago, Yr. Bk. Pub., Mar., 1960, p. 13.

Endo *Complete Information and Reprints on Request*
ENDO LABORATORIES Richmond Hill 18, New York

*Manufactured under license from the Wisconsin Alumni Research Foundation

for a smooth downward curve





New Rautrax-N results in prompt lowering of blood pressure.[1] Rautrax-N, a new antihypertensive-diuretic preparation, provides improved therapeutic action[1] plus enhanced diuretic safety for all degrees of essential hypertension. A combination of Raudixin and Naturetin, Rautrax-N facilitates the management of hypertension when rauwolfia alone proves inadequate, or when prolonged treatment, with or without associated edema, is indicated.

Naturetin, the diuretic of choice, also possesses marked antihypertensive properties, thus complementing the known antihypertensive action of Raudixin. In this way a lower dose of each component in Rautrax-N controls hypertension effectively with few side effects and a greater margin of safety.[1-16]

Other advantages are a balanced electrolyte pattern[1-16] and the maintenance of a favorable urinary sodium-potassium excretion ratio.[2-16] Clinical studies[1-5] have shown that the diuretic component of Rautrax-N—Naturetin—has only a slight effect on serum potassium. The supplemental potassium chloride provides additional protection against potassium depletion that may occur during long term therapy.

Rautrax-N may be used independently or with other antihypertensive drugs, such as ganglionic blocking agents, veratrum or hydralazine, when needed for the occasionally difficult patient.

Supply: Rautrax-N—capsule-shaped tablets providing 50 mg. Raudixin (Squibb Rauwolfia Serpentina Whole Root) and 4 mg. Naturetin (Squibb Benzydroflumethiazide), with 400 mg. potassium chloride.

Dosage: For initial therapy, the suggested dosage is 1 to 4 Rautrax-N tablets daily after meals. If the higher amounts are needed, daily dosage should be divided into 2 doses given every 12 hours. However, dosage should be initiated at a low level, which may be increased after intervals of several days, if necessary, until the desired response is obtained. For maintenance therapy, 1 or 2 Rautrax-N tablets daily should prove adequate; however, daily maintenance dosage may range from 1-4 Rautrax-N tablets. Note: In hypertensive patients already on ganglionic blocking agents, veratrum or hydralazine, the addition of Rautrax-N will require an immediate dosage reduction of each of these agents by at least 50 per cent. The same dosage reduction applies when any of these agents is added to the Rautrax-N regimen. Literature available on request.

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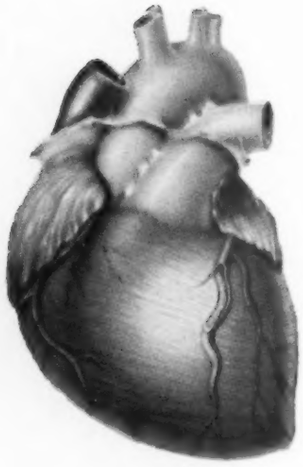
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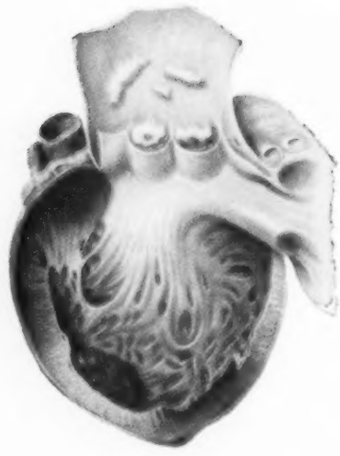
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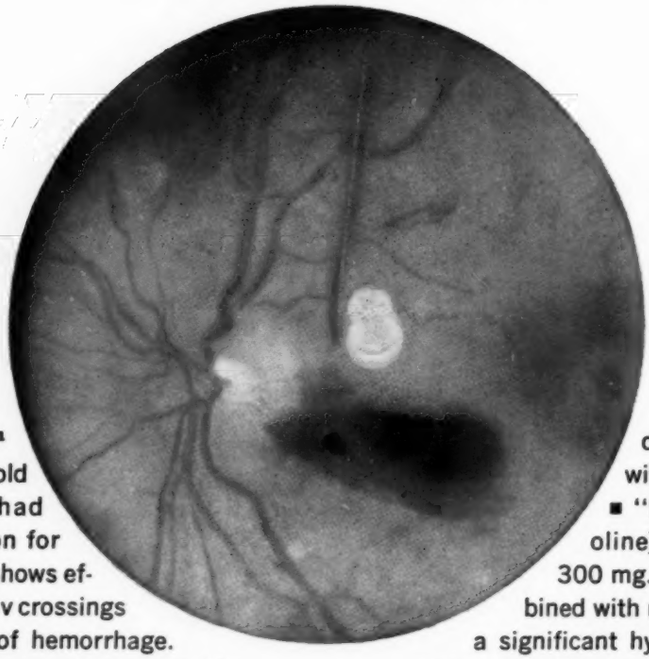
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